ANALYSIS OF RETINAL VASCULAR DENSITY USING OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY, TO DIFFERENTIATE HEALTHY, GLAUCOMA SUSPECT AND GLAUCOMATOUS EYES

DISSERTATION SUBMITTED TOWARDS FULFILLMENT OF THE RULES AND REGULATIONS FOR THE M.S. BRANCH III OPHTHALMOLOGY EXAMINATION OF THE TAMILADU DR. M.G.R. MEDICAL UNIVERSITY TO BE HELD IN MAY 2019

BONAFIDE CERTIFICATE

I declare that this dissertation entitled 'Analysis of Retinal Vascular Density Using Optical Coherence Tomography Angiography, to differentiate Healthy, Glaucoma Suspect and Glaucomatous Eyes' done towards fulfillment of the requirements of the Tamil Nadu Dr. MGR Medical University, Chennai, for the MS Branch III (Ophthalmology) examination to be conducted in May 2019, is the bona fide work of Dr. Bharath Kumar. K, postgraduate student in the Department of Ophthalmology, Christian Medical College, Vellore.

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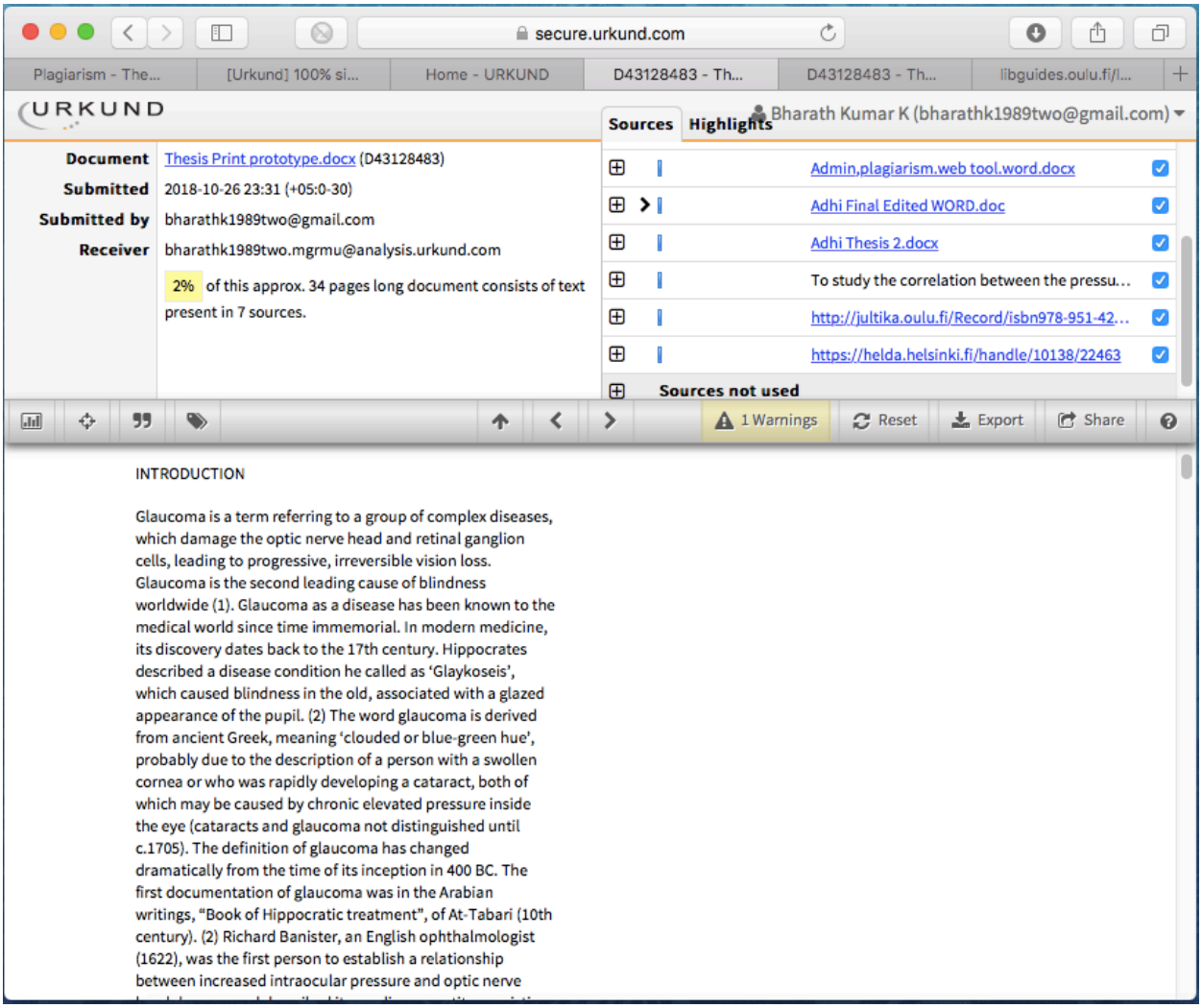

ANTI PLAGIARISM CERTIFICATE

This is to certify that the dissertation work titled "Analysis of Retinal Vascular Density Using Optical Coherence Tomography Angiography, to differentiate Healthy, Glaucoma Suspect and Glaucomatous Eyes" has been submitted by the candidate Dr. Bharath Kumar. K with Registration number: 221613302 for the award of the degree of MS Ophthalmology Branch III. I have personally verified the urkund.com website for the purpose of plagiarism check. I have found that the uploaded thesis file contains from introduction to conclusion and that the result shows 2 % percentage plagiarism in the dissertation.

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INTRODUCTION

Glaucoma is a term referring to a group of complex diseases, which damage the optic nerve head and retinal ganglion cells, leading to progressive, irreversible vision loss. Glaucoma is the second leading cause of blindness worldwide (1).

Glaucoma as a disease has been known to the medical world since time immemorial. In modern medicine, its discovery dates back to the 17th century. Hippocrates described a disease condition he called as 'Glaykoseis', which caused blindness in the old, associated with a glazed appearance of the pupil. (2)

The word glaucoma is derived from ancient Greek, meaning 'clouded or blue-green hue', probably due to the description of a person with a swollen cornea or who was rapidly developing a cataract, both of which may be caused by chronic elevated pressure inside the eye (cataracts and glaucoma not distinguished until c.1705). The definition of glaucoma has changed dramatically from the time of its inception in 400 BC. The first documentation of glaucoma was in the Arabian writings, "Book of Hippocratic treatment", of At-Tabari (10th century). (2)

Richard Banister, an English ophthalmologist (1622), was the first person to establish a relationship between increased intraocular pressure and optic nerve head damage and described it as a disease entity consisting of four features; eye tension, long duration of the disease, the absence of perception of light and the presence of a fixed pupil (2)

In the early 19th century, the first modern description of the disease, and its relation to raised intraocular pressure, was given by Antoine-Pierre Demours (1818). Thereafter, the central concept of a rise in the intraocular pressure being a cause for the changes, became fully established. G.J. Guthrie (1823), in London, established hardness of the eye as characteristic of a disease, which he called Glaucoma. Ultimately, the essential feature of raised intraocular tension was fully established by William McKenzie, the Scottish clinician (1835) who, in his textbook, described the raised tension in both chronic and acute glaucoma.

Another seminal clinical observation in this period was the uniting concept of Donders (1862) where he described a debilitating increased intraocular tension occurring without any inflammatory symptoms as Simple Glaucoma. Drance (1973), for the first time, provided the definition of glaucoma as a disease of the optic nerve (an optic neuropathy), which is caused by a number of factors.

Further advancement in the diagnosis of glaucoma was achieved by the invention of the tonometer, the perimeter and more recently, optical coherence tomography. These tests provide a clinical measurement of integrity of the structure and function of the neural elements damaged in glaucoma, i.e., the retinal ganglion cells and their axons.

Today, despite these advancements, according to the World Health Organization, 55 million people are affected worldwide by Glaucoma (Resnikoff). Twelve million persons worldwide are estimated to be blind because of the disease. It is a disease, which strikes without any warning signs. The visual

impairment is so gradual that the patient may not notice a change in vision until the condition is at an advanced stage and diagnosis is frequently delayed. If glaucoma can be diagnosed early, further vision loss can be slowed or prevented. However, the biological basis of glaucoma is poorly understood and many diagnostic and therapeutic challenges remain. (3) One of the proposed causes for the retinal damage in glaucoma is change in the blood supply and vasculature, at a microscopic level. A vascular etiology for glaucoma has been suspected for many decades. Several investigative modalities have been used to assess the blood flow at the optic disc and peri-papillary retina, in glaucoma patients. But, a gold standard test that provides all the necessary information in one reading has yet to be established to quantify the features of the micro-vascular network.

Optical coherence tomography (OCT) is a relatively new, non-invasive modality in ocular imaging. Using light instead of ultrasound, it provides high-resolution cross sectional images of the optic nerve head, retina and deeper structures. An even more recent advance, derived from OCT is Optical Coherence Tomography Angiography (OCTA) which is helping us study retinal blood flow using the principle of studying de-correlation between the signals of OCT cross-sectional scans repeated at the same location, caused by blood flow, thus providing a detailed view of the vascular structures in the retina and optic nerve head. This technology has the advantage of being noninvasive, rapid and reproducible.

Using OCTA (DRI-TRITON Plus), in our study, we analyze and compare the vascular density in the optic disc, papillary and peri-papillary areas in normal

eyes, glaucoma suspects (Ocular hypertensives) and in diagnosed early glaucoma patients. This investigation modality, though widely used to study retinal microcirculation, has not been extensively studied for its effectiveness in the diagnosis and prognostication of glaucoma, in the Indian population.

AIM

To analyze retinal vascular density using swept source optical coherence tomography angiography (OCTA) in patients with early primary open angle glaucoma (POAG), Glaucoma suspects (Ocular Hypertensives), and normal eyes.

OBJECTIVES

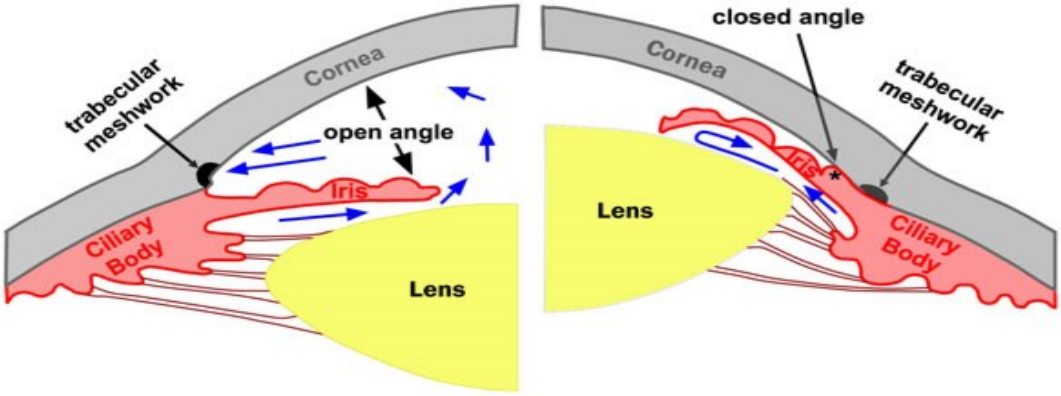
1. To analyze and compare Vascular density index in the optic disc, papillary area and peri-papillary area, using OCTA, in Normals, Glaucoma suspects (Ocular Hypertensives) and diagnosed early POAG patients.

2. To investigate the correlation between retinal vessel density measurements and other parameters like retinal nerve fiber layer thickness and visual field changes (mean deviation) on automated perimetry.

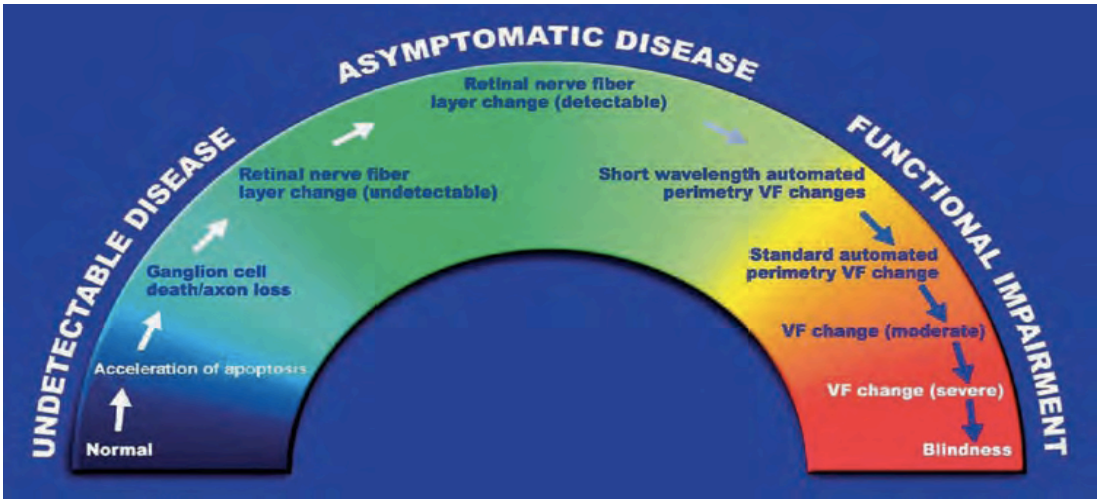
REVIEW OF LITERATURE

Glaucoma is a chronic, progressive optic neuropathy caused by a group of ocular conditions, which lead to damage of the optic nerve with characteristic changes of the optic nerve head, and corresponding visual field defects, (4) with intraocular pressure (IOP) the only modifiable risk factor and IOP reduction the only treatment. The nerve damage results from loss of retinal ganglion cells (RGC) (5-8)

Types of glaucoma



Colour Plate 1: **Open angle type (left) and closed angle type (left)**



Colour Plate 2: **The glaucoma continuum (9)**

Disease burden

Glaucoma is the second leading cause of blindness worldwide. Twelve million persons worldwide are estimated to be blind because of the disease. (4) With the exception of Asia, Primary open angle glaucoma (POAG) is far more common than Primary angle-closure glaucoma (PACG), accounting for around three fourth of all glaucoma cases worldwide. (10) In Asia, population-based studies from China and India have reported that a significant percentage of the population suffers from angle-closure glaucoma. (11-16).

More importantly it is the most common cause of irreversible blindness in the world and it is estimated that more than 3 million people are blind due to this disease. (17)

The estimated prevalence of the disease in the word was 60.5 million in 2010, and is expected to rise to 79.6 million by 2020 (10) Several population based studies have been conducted to throw light on the prevalence of glaucoma in India, important among them are: -

1. Vellore Eye Study (VES)
2. Chennai Glaucoma Study (CGS)
3. Andhra Pradesh Eye Disease Study (APEDS)
4. West Bengal Glaucoma Study (WBGS)
5. Aravind Comprehensive Eye Survey (ACES)

Study	Study Period	Setting	Age Group	Number Examined (Response Rate %)	Diagnostic Criteria		
					IOP	Optic Disc	Visual Fields
VES	1994	Urban	30-60	972 (50.3)	±	+	+
APEDS	1996-2000	Urban	All ages	10,273 (87.3)	–	+	±
ACES	1995-97	Rural	40+	5150 (93.0)	–	+	±
CGS	2001-04	Rural, Urban	40+	7774 (81.0)	–*	+	±
WBGS	1998-99	Rural	50+	1324 (83.1)	–*	+	±

*The CGS and the WBGS used the ISGEO[15] criteria (with minor modifications) to diagnose disease. An IOP level that exceeds the 99.5th percentile for a normal population is used to diagnose disease only when the optic disc cannot be visualized and visual fields are not possible.

ACES indicates the Aravind comprehensive eye survey; APEDS, the Andhra Pradesh eye disease study; CGS, the Chennai glaucoma study; ISGEO, international society of geographical and epidemiologic ophthalmology; VES, Vellore eye study; WBGS, West Bengal glaucoma study.

Table 1: Summary of different population based studies from India (68)

Population Based Studies	Primary Open Angle Glaucoma (POAG)	Primary Angle Closure Glaucoma (PACG)
APEDS	2.65	1.11
ACES	1.29	NR
CGS (rural)	1.85	0.98
CGS (urban)	4.24	0.74
WBGS	1.81*	0.15*

NR: Not reported/ age wise prevalence not reported. VES data not available.

ACES indicates the Aravind comprehensive eye survey; APEDS, the Andra Pradesh eye disease study; CGS, the Chennai glaucoma study; VES, Vellore eye study; WBGS, West Bengal glaucoma study.

*WBGS data reported only for the 50+age.

Table 2: Age Standardized Rates for POAG and PACG for the Population Aged Above 40 y (Standardized to the Population of India 2008 Population Estimates) (68)

	APEDS (n = 934)	ACES (n = 5150)	CGS (Rural) (n = 3924)	CGS (Urban) (n = 3850)	WBGS (n = 1269)
40-49	1.27	0.34	0.63	2.26	—
50-59	2.31	1.57	1.62	3.57	2.55
60-69	4.89	1.83	2.58	4.08	2.69
70+	6.32	2.88	3.25	6.42	4.76
Reported prevalence % (95%CI)	2.56 (1.22,3.91)	1.7 (1.3,2.1)	1.62 (1.42,1.82)	3.51 (3.04,4.0)	2.99

VES reported prevalence (30 to 60 y): 0.41%(95%CI: 0.08,0.81).

ACES indicates the Aravind comprehensive eye survey; APEDS, the Andra Pradesh eye disease study; CGS, the Chennai glaucoma study; CI, confidence interval; RUR, rural; URB, urban; VES, Vellore eye study; WBGS, West Bengal glaucoma study.

Table 3: Age Wise Prevalence of Primary Open Angle Glaucoma in Different Studies (68)

In India, the disease burden due to glaucoma is severe, accounting for about one fifth of the global burden. Even though two third of all glaucoma cases in Caucasians are primary open angle glaucomas, studies show that the

Indian population has an equal proportion of open and close angle glaucomas. (10)

The prevalence of POAG in south India, among the rural population, aged 40 and above, was 1.7% according to the AECS. (18) This was in contrast to the observations in the urban south Indian population, which showed a prevalence of 3.5% in the Chennai Glaucoma Study. (19). A more alarming fact discovered in these surveys, was that greater than 90% of the glaucoma cases were lying undiagnosed and were identified only during the surveys (93% in ACES and 98.6% in the Chennai Glaucoma Study). The National Blindness survey, conducted in 2001, showed that glaucoma is the third major cause of irreversible blindness in India and responsible for 5.9% of blindness (i.e., visual acuity of <6/60) (20). The recent surveys have shown a threefold increment in blindness due to glaucoma as found in previous surveys and literature (21)

Despite all this, we are of the opinion that blindness due to glaucoma is grossly underestimated as most of these surveys have defined blindness based on visual acuity alone and have not given equal importance to visual fields, which form one of the defining criteria for glaucoma. Hence in order to identify more cases correctly, we need to start from understanding the anatomy, physiology of the optic nerve head and retinal ganglion cells, their blood supply, pathogenesis and progression of glaucoma as a disease. The understanding of the above will aid in correlating the findings in the investigation being studied.

Aqueous secretion and outflow (22)

Aqueous humour is produced, from the ciliary processes, in two steps, i.e., formation of a plasma filtrate within the stroma of the ciliary body and formation of aqueous from this filtrate across the blood-aqueous barrier.
This occurs by active and passive processes.

The aqueous outflow occurs from the posterior chamber via the pupil into the anterior chamber, to the angle of the anterior chamber. From here, the exit occurs, in its most part, through the sieve-like trabecular meshwork, at the angle of the anterior chamber (consisting of the uveal, corneoscleral and juxtacanalicular meshworks), and the Schlemm canal (Trabecular or conventional outflow 90%) and partly through the Uveoscleral route (10%).

Intraocular pressure (23)

The intraocular pressure is decided by the balance between the rate of aqueous production and outflow. The latter is in turn determined by the resistance encountered in the outflow channels and to the level of episcleral venous pressure.

The distribution of IOP within the general population falls within the range of 11–21 mmHg. Although there is no definite pathological cutoff point, 21 mmHg is considered the upper limit of normal and levels above this warrant investigation. However, in some patients glaucomatous damage occurs with

IOPs less than 21 mmHg (normal-tension glaucoma) whilst others remain unaffected with IOPs as high as 30 mmHg (ocular hypertension). Although the actual level of IOP is a cornerstone in the development of glaucomatous damage, other factors are also significant. There can also be variations in IOP with time of day, blood pressure, respiration, valsalva etc. A diurnal variation of up to 5 mm hg may be seen in normal eyes, and fluctuations greater than this are suspicious of glaucoma.

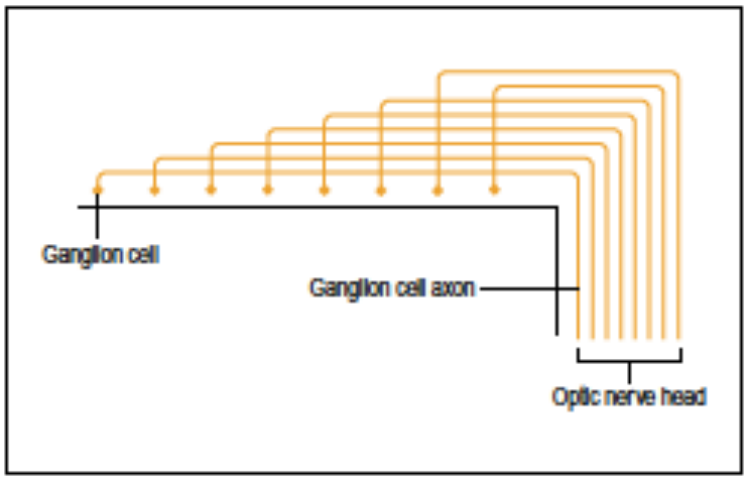
Normal optic nerve head (24)

The optic nerve head (ONH) or the optic disc consists of the neuroretinal rim and the optic cup. The neuroretinal rim (NRR) is the rim of tissue between the optic disc margin and the outer edge of the optic cup. It is normally described as pink or orange in colour with the inferior rim being the broadest. The optic cup is the central depression seen within the confines of the NRR. The normal size of the cup is largely determined by the size of the disc itself, the smaller discs having smaller cup sizes and vice versa.

The ONH can be divided into four cross-sectional parts: the surface layer and the prelaminar, laminar, and retrolaminar portions, each with its own blood supply and glial tissue.

The arrangement of the axons of the retinal ganglion cells from the peripheral retina toward the optic nerve is such that axons from peripheral ganglion cells are progressively over-layered by axons derived from cell bodies closer to the optic nerve. These peripheral fibers remain peripheral as they enter

the disc; central fibers enter centrally, lying closer to the physiological cup. This arrangement is responsible for the manner of clinical progression of the glaucomatous field defect; i.e., paracentral scotomas appear early.



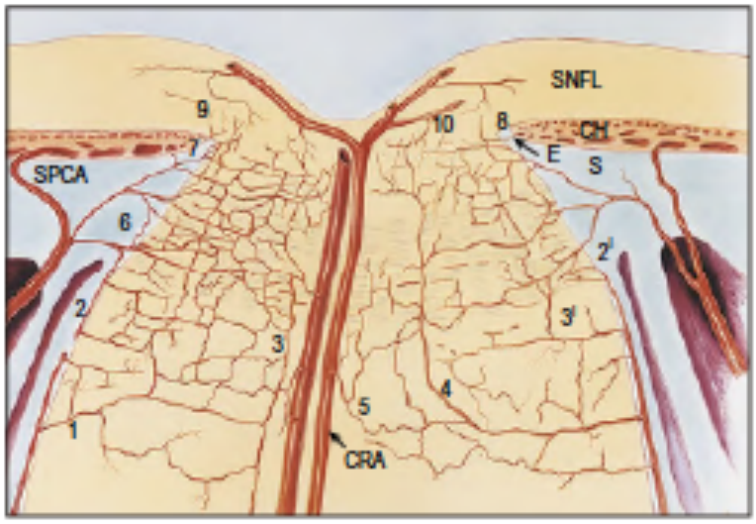
Colour Plate 3: Schematic diagram of the axonal arrangement at optic nerve head (33)

Blood Supply **(25-32)**

The central retinal artery (CRA) and the short posterior ciliary arteries (SPCAs), together form a capillary plexus that supplies the ONH. The venous drainage of the ONH is almost entirely through branches of the central retinal vein, although important choroidal collaterals exist, which open up in case of any disturbance to the normal channels.

The surface layer of the ONH is supplied by the central retinal artery (responsible for flame shaped haemorrhages seen clinically); prelamiinar part is supplied by branches from the short posterior ciliary arteries. Most studies believe that vessels derived from the peripapillary choroid make only a minor

contribution to the blood supply of the anterior ONH. The laminar portion is supplied by centripetal SPCAs, and also a longitudinal anastomotic capillary bed. The anterior portion of the retrolaminar nerve has both, centripetal branches from the pia-meninges, and also branches from the central retinal artery.



Colour Plate 4: Composite illustration of the various optic nerve vascular arrangements (25)

The pathogenesis of glaucomatous damage is attributed to a combination of factors affecting axonal health, with each factor being interlinked in its effects to all the others.

The two main influences are:

- Mechanical changes due to the rise of intraocular pressure
- Vascular perfusion of the optic nerve head.

GLAUCOMA: A Vascular Dysregulation

The Optic nerve head and RNFL is largely comprised of the axons of RGCs, one of the most metabolically active cells in human body. These cells have tremendous metabolic requirements and depend on regional capillary networks to meet them.

Several studies have reported that vascular factors may play a critical role in the development of glaucoma in addition to elevated IOP (6-8, 34, 35) and have demonstrated reduced ocular blood flow in optic nerve head and retinal circulation in glaucoma. (36-47)

The perfusion of the optic nerve head may be affected because of a lack of an adequate auto regulatory mechanism. A substantial rise in intraocular pressure can also decrease the capillary blood flow due to mechanical compression of vessels at the lamina cribrosa or a decreased flow in the annulus of Zinn, which supplies nutrition to the laminar and post-laminar optic nerve head. A fall in perfusion pressure at the optic disc may additionally be caused by systemic factors such as hypotension, vasospasm and acute blood loss. (4)

Generalized narrowing of the retinal vessels has been found in cases with advanced glaucomatous damage. Before the availability of semi-automated machines, retinal vessel calibers in glaucoma patients were measured via manual means. (41, 46, 48)

The reduction in caliber was seen more in arteries than in veins, with areas of greater ONH damage and thinner retinal nerve fibers, showing reduced caliber. An attempt is made to explain this association between area of ONH damage and reduction in vessel caliber: -

One opinion is that, Retinal ganglion cell loss has been suggested to result in vasoconstriction as an adjustment to reduced metabolic demand. This is in agreement with the observation of retinal arterial narrowing in patients with non-glaucomatous optic atrophy. (62–64)

Alternatively, the other opinion is that, the underlying pathological process leading to RGC loss is related to impaired local auto regulation, vasoactive substance leakage and consequently vasoconstriction. (46, 49, 50, 51).

Population based studies have also further seconded the above findings. The Blue Mountains Eye Study (BMES) showed that patients with POAG were 2.7 times more likely to show generalized retinal arteriolar narrowing than patients without glaucoma. This remained true after adjusting for risk factors for glaucoma and is independent of ocular perfusion pressure. (52). The Singapore Malay Eye Study found consistently, a relationship between quantitatively measured retinal vascular caliber and prevalence of glaucoma and larger

vertical cup–disc ratio (CDR) (53). Yoo et al reported similar findings of retinal arteriolar narrowing in glaucomatous eyes, and further found that thinning of retinal arteriolar caliber was comparable to thinning of retinal nerve fiber layer in detecting open angle glaucoma (54).

Thus, population-based and hospital-based cross-sectional studies have largely supported the association between narrowing of retinal vessel caliber and glaucoma.

Several non-invasive and invasive techniques have been developed to study optic nerve head and peri-papillary retinal blood flow.

Noninvasive techniques

- Color Doppler imaging (CDI),
- Laser Doppler Velocimetry (LDV)
- Laser speckle technique
- Laser Doppler Flowmetry (LDF)
- Retinal vessel analyzer (RVA)
- Retinal oximetry
- Blue field entoptic technique.

Invasive techniques

- Scanning laser ophthalmoscopy angiography with fluorescein and/or Indocyanine green (ICG) dye.

Most of the studies using available technologies demonstrated reduced blood supply in the optic nerve and peri-papillary retina of glaucoma patients and some confirmed a correlation between severity of the disease and the degree of hemodynamic disturbance. (34, 55-58)

Despite the critical role of the capillary plexus in the optic nerve head and RNFL changes, leading to glaucomatous damage, suggested by several investigators, our previous inability to quantify micro vascular network density features, and the lack of a reproducible and relevant in vivo quantitative assessment method, has prevented evaluation of the clinical characteristics of the capillary beds, at a microscopic level and obtaining a more comprehensive understanding of the RGC axonal damage in glaucoma.

A reliable clinical method for imaging these vascular beds would improve our knowledge about the role of capillary vascular plexus in RGC axonal health and disease. (59)

Functional changes, as assessed by automated perimetry or visual field testing, occur only after 40% of RGC loss, which is quite late. Hence methods to detect any insults occurring early on in glaucoma, before functional/ field changes develop are important.

Also, better understanding of the vascular changes in patients with

glaucoma, can give rise to other management options, especially in patients who show progressive glaucomatous damage despite adequate lowering of IOP.

Fluorescein angiography can provide useful information about the vasculature of the optic disc, but this is an invasive test with its own complications and also, the information obtained is limited to the larger vessels only. A high-resolution image of the papillary and peri-papillary microvasculature cannot be practically obtained. Spaide et al (60) obtained spectral domain OCT Angiography images from the ONH of 12 healthy subjects and compared the peri-papillary capillary network with images obtained by fluorescein angiography. They reported that the radial peri-papillary capillary network could not be visualized by fluorescein angiography, whereas the network was readily visualized in OCT Angiography images.

Optical Coherence Tomography (OCT)

Optical coherence tomography (OCT) is a non-invasive, non-contact imaging system, which provides high-resolution cross-sectional images of the retina, vitreous, and optic nerve head.

OCT technology uses low-coherence interferometry to capture high-resolution cross-sectional images of tissue morphology, providing images to derive an optical biopsy section. It is analogous to ultrasound except it uses

light instead of sound. Low-coherence near-infrared light is produced by a diode light source, and transmitted to the retina via a fiber optic delivery system. The backscattered rays from the retina are captured and utilized to construct a cross-sectional tomographic image of the retinal area analyzed. It permits a dynamic, real time imaging of retina and its pathology, and also provides quantitative information about retinal architecture at high resolution. (61)

The following imaging strategies are applicable to glaucoma:

1. Peri-papillary retinal nerve fiber layer. This involves the acquisition of a circular scan of diameter 3.4 mm of the retina around the optic nerve head. Retinal thickness is compared with normals. Sensitivity and specificity are around 90%.
2. Optic nerve head. Radial cross-sectional scans permit an objective and repeatable assessment of disc morphology, with reasonable discriminatory value. This function has tended to be less commonly used than RNFL analysis in practice.

OCT gives an objective measurement of retinal nerve fiber layer (RNFL) thickness and/or ganglion cell complex (GCC), which is important for glaucoma assessment. The commercially available spectral domain (SD)-OCT offers benefits in glaucoma assessment over the earlier generation of time domain-OCT due to increased axial resolution, faster scanning speeds and has

been reported to have improved reproducibility but similar diagnostic accuracy. Newer advances in OCT technology have enabled increases in scanning speed to 20,000– 50,000 A-scans/second and even up to 100,000 A-scans/second, to produce of a truly three dimensional image of the site of interest with reproducible registration, and advanced segmentation algorithms of macular and optic nerve head regions. It allows visualization of the individual retinal layers, comparable to a conventional histopathology section. But it has limited utility in advanced disease and does not relate to cause of disease as opposed to the final presentation. (62)

Optical Coherence Tomography Angiography (OCTA) In Glaucoma

Optical coherence tomography angiography is an emerging technology, with the potential to lead to a paradigm shift in glaucoma diagnostics.

OCTA is a new, non-invasive imaging technique that generates volumetric angiography images in a matter of seconds. OCTA is quick and non-invasive, and provides volumetric data with the clinical capability of specifically localizing and delineating pathology along with the ability to show both structural and blood flow information.

It was described first in 2006 but its use in ocular diseases started to be explored only in 2013. The technology first became commercially available for use in practice, only in 2014 with the introduction of the Avanti OCT-A

(Optovue Inc., USA) (34)

Unlike traditional angiography with fluorescein, this technology does not require the injection of extrinsic contrast agent. OCTA detects the motion of red blood cells as intrinsic contrast and is sensitive to both transverse and axial flow in time. This is made possible by the use of high speed of Fourier-domain OCT (>50 kHz), which allows multiple cross-sectional images to be obtained at the same location to detect relative motion in vessels which can be superimposed to give color-coded flow information over gray scale structural information. Thus, both blood flow and retinal structural information may be presented together. OCTA generates a data cube, segmentation, and en face presentation of vascular perfusion at various layers of the retina and can summarize the flow information at relevant anatomic layers or slabs. These en face images can then be used to visualize the individual vascular plexuses at various levels of depth depending on the condition of interest.

Of practical importance is the fact that existing OCT machines can be upgraded to perform angiography and use either the Doppler shift or variations in speckle pattern. Both varieties of Fourier-domain OCT, spectral or swept source are used.

Split-spectrum amplitude decorrelation angiography is an algorithm that is capable of flow detection at both the ONH and at the macula and quantifies

the data as both flow index and vessel density.

For diagnosis in patients with retinal pathologies, the introduction of OCT-A has been a huge advancement as it provides both functional and morphological analysis of the retina from a single dye-less examination. In the case of ONH microvasculature, the network is so fine and tightly arranged that it could not been visualized with traditional fluorescein angiography. OCT Angiography provides more confidence than the tried and tested, older testing methods. (63)

There are several studies, which have used OCTA to evaluate the vascular changes in early glaucoma patients, suspects and normals.

Adeleh Yarmohammadi et al (57) studied Two hundred sixty-one eyes of 164 healthy, glaucoma suspect, and open-angle glaucoma (OAG) participants, and found that age-adjusted mean vessel density was significantly lower in OAG eyes compared with glaucoma suspects and healthy eyes. Optical coherence tomography angiography vessel density had similar diagnostic accuracy to RNFL thickness measurements for differentiating between healthy and glaucoma eyes.

Liang Liu et al (64) studied 12 glaucomatous eyes and 12 age-matched normal eyes, and found a dense micro vascular network around the disc in normal eyes, compared to visibly attenuated micro vascular network in glaucomatous

eyes. They concluded that reduced peri-papillary retinal perfusion in glaucomatous eyes can be visualized as focal defects and quantified as peri-papillary flow index and peri-papillary vessel density, with high repeatability and reproducibility.

Handan Akil et al (65) studied 56 eyes in total (20 eyes with mild POAG, 20 pre-perimetric glaucoma eyes, and 16 age-matched normal eyes as controls) and found a statistically significant difference for the peri-papillary vessel density, optic nerve head vessel density, and papillary vessel density among all the groups, and concluded that the three groups could be differentiated on the basis of OCTA derived retinal vessel density measurements.

C. Lommatzsch et al (66) studied a total of 68 eyes (34 eyes diagnosed with glaucoma and 34 healthy control eyes) and demonstrated that peri-papillary total flow density was significantly different in glaucoma eyes from healthy eyes.

These studies have all been done in Caucasian eyes. We want to acquire more data about the perfusion of the optic disc and peri-papillary retina in glaucomatous eyes in the Indian population.

Based on this current study, we aim to develop OCT-A as a new imaging target for early diagnosis and management of glaucoma.

MATERIALS AND METHODS

This is a prospective, observational study, conducted in the out-patient department of a tertiary eye care hospital namely- Department of Ophthalmology, Schell Eye Hospital, CMC Vellore, This study is done by capturing and analyzing OCT angiography images, comparing differences in retinal vascular densities with the OCT RNFL thickness (structural parameter) and Visual field testing results (functional parameter) between the three groups namely normal, glaucoma suspects (Ocular hypertensives) and diagnosed glaucoma patients. There will be no follow up required. All investigations will be completed in the same visit.

Participants:

All glaucoma suspects (Ocular hypertensives), age matched normals and diagnosed glaucoma patients between 30- 60 years of age fulfilling the inclusion criteria and willing to participate were invited to participate in the study. Notices were posted in all the outpatient rooms to remind doctors to refer patients for study. Those patients, who were willing, then underwent a detailed eye examination with their respective doctors and then referred to the Primary Investigator (PI) for this study.

The PI then got an informed consent from the participant. PI assessed the patient's eligibility to be recruited in the study, based on the inclusion and exclusion criteria mentioned below. Informed consent was taken in Tamil or English depending on the language they could understand.

INCLUSION CRITERIA

Diagnostic criteria for glaucoma patients: -

1) The presence of characteristic glaucomatous optic disc damage and abnormal thinning of the circum-papillary RNFL;
2) Visual field defects consistent with glaucoma, confirmed on at least two visual field examinations; only mild- moderate stage POAG eyes based on Hoddap-Anderson-Parrish scale were included in our study as measured by visual field mean deviation scores (MD up to -12.0 dB).
3) Open angles on gonioscopy;
4) Patients who had been diagnosed as POAG before and were already on anti-glaucoma medications.
5) No history of any other ocular or systemic diseases causing non-glaucomatous optic nerve damage.

Diagnostic criteria of glaucoma suspects: -

1) Patients who did not meet the previously stated definition of glaucoma.
2) IOP >21 mm of hg (Ocular hypertension)
3) Absence of clinically detectable glaucomatous optic nerve damage, or retinal nerve fiber layer defects.
4) Absence of detectable visual field defects.

Diagnostic criteria for the normals (Controls): -

1) IOP of < 21 mmHg,
2) Normal appearing optic nerve head, intact neuroretinal rim

3) Normal RNFL thickness.
4) Normal standard automated perimetry (defined as a glaucoma hemi field test within normal limits and a pattern standard deviation within 95% confidence-interval limits)

Exclusion criteria FOR ALL CATEGORIES

(1) Best-corrected visual acuity less than 6/18,
(2) Age younger than 30 years or older than 70 years,
(3) Refractive error greater than +3.00 diopter (D) or less than − 6.00 D,
(4) Previous intraocular surgery except for uncomplicated cataract extraction with posterior chamber intraocular lens implantation (less than 3 months post any intraocular procedure).
(5) Any fundus pathology – Age related Macular degeneration, Diabetic retinopathy (Any stage), and Vein and artery occlusions.
(6) Disc pathologies, non-glaucomatous conditions that may cause optic disc abnormalities
(7) Non-glaucomatous conditions that may cause VF loss (Optic neuritis, anterior ischemic optic neuropathy, Retinitis pigmentosa, optic pathway lesions)
(8) Inability to perform reliably, on automated visual field-testing.

One eye from each participant was imaged and analyzed in a random manner.

The following variables were defined before measurement:

Visual field Mean Deviation (dB)

Overall mean deviation indicates any overall depression (or elevation) of the patient's hill of vision. A positive number indicates a better than normal field (elevation of the hill of vision). A negative number indicates a depression of hill of vision. It is categorized as normal, or abnormal at a p-value of 5, 2, 1, or 0.5%, which lower p values corresponding with greater clinical significance and a lower likelihood that the result occurred by chance.

Visual field Pattern Standard Deviation (dB)

Indicates any isolated differences in a particular field. It highlights any irregularity in the visual field, irrespective of any overall depression. Overall pattern standard deviation is categorized as normal, or abnormal at a p-value of 5, 2, 1, or 0.5%, which lower p values corresponding with greater clinical significance and a lower likelihood that the result occurred by chance.

Cup/Disc Ratio

Ratio of the vertical size of the cup (in mm) to the vertical size of the entire disc (in mm)

Mean RNFL thickness (µm)

The mean of the retinal nerve fiber layer thickness, calculated by the OCT machine

Superior RNFL thickness (µm)

Mean of the retinal nerve fiber layer thickness, in the superior hemi-retina.

Inferior RNFL thickness (µm)

Mean of the retinal nerve fiber layer thickness, in the inferior hemi-retina.

Optic nerve head area vessel density (%) (VdONH)

Density of the microvasculature at the optic nerve head area, which will be calculated by image analysis.

Peri-papillary area vessel density (%) (VdPPA)

Density of the microvasculature at the peri-papillary area (700-micron wide elliptical annulus centered on the disc), which will be calculated by image analysis.

Papillary area vessel density (%) (VdPA)

Density of the microvasculature at the papillary area (3 mm circular region centered on the ONH), which will be calculated by image analysis.

Superior Papillary area vessel density (%) (VdSPA)

Density of the microvasculature at the superior papillary area (superior hemi-retina), which will be calculated by image analysis.

Inferior Papillary area vessel density (%) (VdIPA)

Density of the microvasculature at the inferior papillary area (inferior hemi-retina), which will be calculated by image analysis.

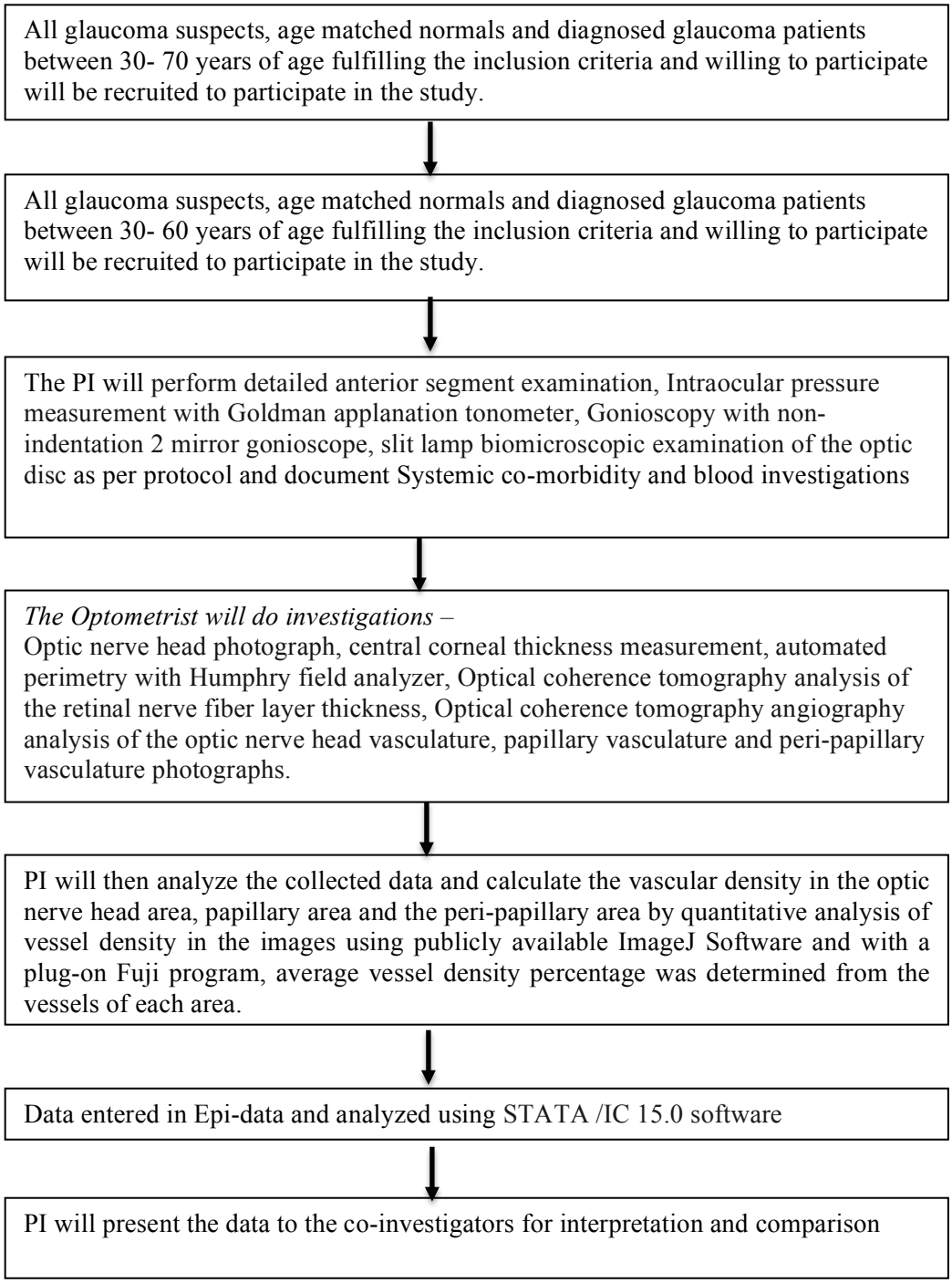
Diagnostic Criteria –

Table 4: Glaucoma Grading Scale (Hodapp-Anderson-Parrish Criteria) (67)

Stage	**Humphrey MD score**	**Additional Criteria (At least 1 of the listed criteria must apply)**
Stage 0: No or Minimal Defect		
Stage 1: Early Defect	≥ -6.00 dB	• A cluster of ≥ 3 points on the pattern deviation plot in an expected location of the visual field depressed below the 5% level, at least one of which is depressed below the 1% level • CPSD/PSD significant at P<0.05 • GHT Outside Normal Limits
Stage 2: Moderate Defect	≥ -6.00 to -12.00 dB	• ≥ 25% but <50% of points on the pattern deviation plot depressed below the 5% level, and ≥15% but <25% of points depressed below the 1% level • At least 1 point within the central 5° with sensitivity of <15 dB but no points in the central 5° with sensitivity of <0 dB • Only 1 hemi field containing a point with sensitivity <15 dB within 5° of fixation
Stage 3: Advanced Defect	≥ -12.01 to -20.00 dB	• ≥ 50% but <75% of points on pattern deviation plot depressed below the 5% level and ≥25% but <50% of points depressed below the 1% level • Any point within the central 5° with sensitivity <0 dB • Both hemi fields containing a point(s) with sensitivity <15 dB within 5° of fixation
Stage 4: Severe Defect	≥ -20.00 dB	• ≥ 75% of points on pattern deviation plot depressed below the 5% level and ≥50% but <50% of points depressed below the 1% level • At least 50% of points within the central 5° with

		sensitivity <0 dB • Both hemi fields containing >50% of points with sensitivity <15 dB within 5° of fixation
Stage 5: End-Stage Disease		Unable to perform HVFA in worst eye due to central scotoma or worst eye VA 6/60 or worse due to POAG. Fellow eye may be at any stage

DETAILED DIAGRAMMATIC ALGORITHM OF THE STUDY



STUDY METHODOLOGY:

After taking the Informed consent, data regarding inclusion and exclusion criteria was obtained by a detailed history and clinical examination of the patients by the PI. Data regarding confounding factors was obtained by a detailed questionnaire.

Potential confounders – include age, gender, diabetes mellitus, hypertension, hypercoagulable states and systemic medications.

The patients who were found suitable for the study were asked a few questions regarding their demographic Data, like Age, Gender, Phone Number, Address, Hospital Number, Ocular complaints, if any, past history of any ocular surgery/treatment, systemic co-morbidities of patients suffering from Diabetes Mellitus (DM), Hypertension (HTN), Ischemic Heart Disease (IHD), Asthma and the duration of their present ailments were also noted. If the patient is already a diagnosed Glaucoma patient, then name and number of anti- glaucoma medications that are being taken and duration of use were noted by PI and all the data captured was entered in the proforma and stored in separate files.

Then the patients underwent detailed anterior segment examination, Intraocular pressure measurement with Goldman applanation tonometer, Gonioscopy with non-indentation 2 mirror gonioscope, slit lamp biomicroscopic

examination of the optic disc, disc photograph, Disc diameter measurement and the readings were entered by PI in the proforma.

Data Sources/measurement

- Ocular examination, measurement of IOP and gonioscopy, was done by the PI.
- Intra-ocular pressure was measured by Goldman applanation tonometry (Model AT 900) with a Haag Streit slit lamp biomicroscope (BM 900), which is the gold standard for IOP measurement.
- Gonioscope used was a 2 mirror non-indentation indirect gonioscope (Volk G-2 Two-Mirror Glass Gonio Lens, Germany)

All Measurements were done by the primary investigator and in the same machine.

Investigations performed by trained and experienced optometrist:

- CCT (Central Corneal Thickness) measurement by Tomey ultrasound instrument.

- Visual field tests were performed with the Humphrey Field Analyzer II (Carl Zeiss Meditec, Inc). The system was set for the 24±2 threshold test, size III white stimulus, and SITA-standard algorithm.

- RNFL (Retinal Nerve Fiber Layer) thickness, from a 3.4-mm diameter circle scan centered on the disc, was assessed with SD-OCT (TOPCON DRI OCT Triton Plus).

- Optical coherence tomography angiography (OCT-A) scans were performed using the Swept- Source Optical Coherence Tomography (SSOCT-A -- DRI OCT TRITON Plus, TOPCON Inc, Tokyo, Japan) with a central wavelength of 1050 nm light source and scanning speed of 100,000 A scans/ sec. The optic disc region was imaged using a 3 x 3 mm scan. Custom grading software of the device used to generate the maps. En-face images of the vasculature were generated from the optic nerve and retinal layers and collapsed into a single two-dimensional image set, between the internal limiting membrane and retinal pigment epithelium using automated layer segmentation OCT instrument software (IMAGEnet 6 V.1.14.8538).

IMAGE PROCESSING AND QUANTITATIVE ANALYSIS:

En face scans that were acquired in the glaucoma suspects, age matched controls and glaucoma patients were further processed and quantitative analysis of the vessel density performed using the publicly available ImageJ software.

Vessel density ratio for each region of interest was calculated by dividing the vessel area by total area of the entire image *100 % using Fuji Program (Plug-in Module for ImageJ software). This was done for the entire image as well as 3 regions of interest: -

1) Papillary region (3 mm circular region centered on the ONH),
2) Peri-papillary region (700-micron wide elliptical annulus centered on the disc)
3) The optic nerve head

Also, since mild glaucoma often presents with focal, rather than global defects, we divided the vessel intensity ratio for the papillary region into superior and inferior domains and then performed the calculations.

ANALYSIS OF IMAGE USING IMAGEJ SOFTWARE

ImageJ is an free, open source, Java-based image processing program developed at the National Institutes of Health and the Laboratory for Optical and Computational Instrumentation (LOCI, University of Wisconsin).

It can display, edit, analyze, process, save, and print 8-bit color and gray scale and various other types of images and can be used to manipulate these images to calculate area and pixel value statistics of user defined selections.

The vessel analysis protocol uses the following formula to calculate vessel density metrics: -

$$\text{Vascular Density} = \frac{\text{Vessel Area}}{\text{Total area of image}} \times 100$$

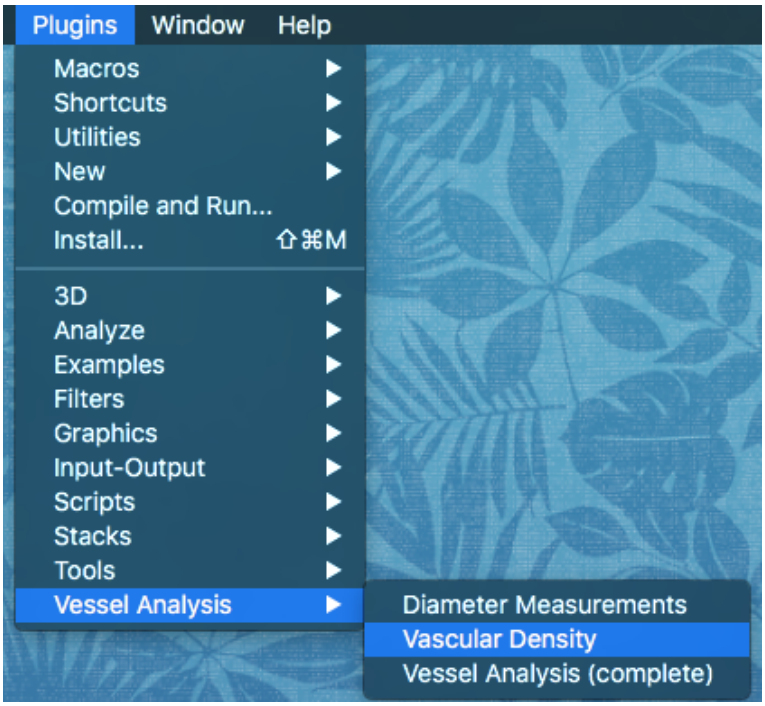
Firstly, The ImageJ software is to be downloaded and installed onto the computer, along with the Vessel analysis plugin. (Both available publicly, as open source, free of cost). Once the plugin is installed, the vessel analysis tab will appear listed near the bottom of the 'Plugins' drop down menu.

Available here: -

http://imagej.net/Fiji/Downloads

http://imagej.net/File:Vessel_Analysis.zip

Colour Plate 5: ImageJ Software desktop program application window



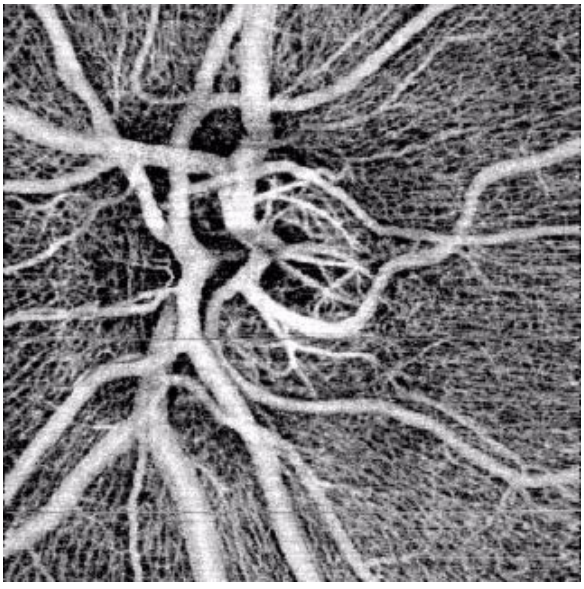
Colour Plate 6: Location of Vascular density tab, in the tool bar

The layout of the image acquisition and viewing software in the OCT Angiography machine (Topcon DRI OCT Triton plus) shows all the OCTA images at different sections.

In the first square, seen to the left, we set the thickness of the section to include all the layers/scans from Internal limiting membrane to retinal pigment epithelium, thus creating a composite image containing the combination of all the microvasculature maps captured at different levels by the machine, between the two set boundaries.

Colour Plate 7: Layout of data viewer on DRI OCT Triton plus, showing the microvascular network in OCTA images at different sections, the colour vessel density map, and the colour disc photograph

The composite image formed is like so: -

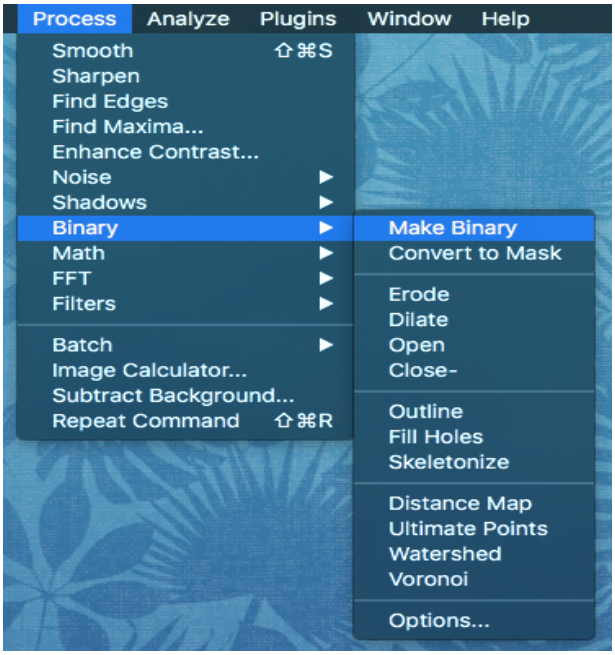


Colour Plate 8: 2-dimentional composite OCTA image formed by superimposition of the micro vascular network maps of all the sections acquired between internal limiting membrane to retinal pigment epithelium.

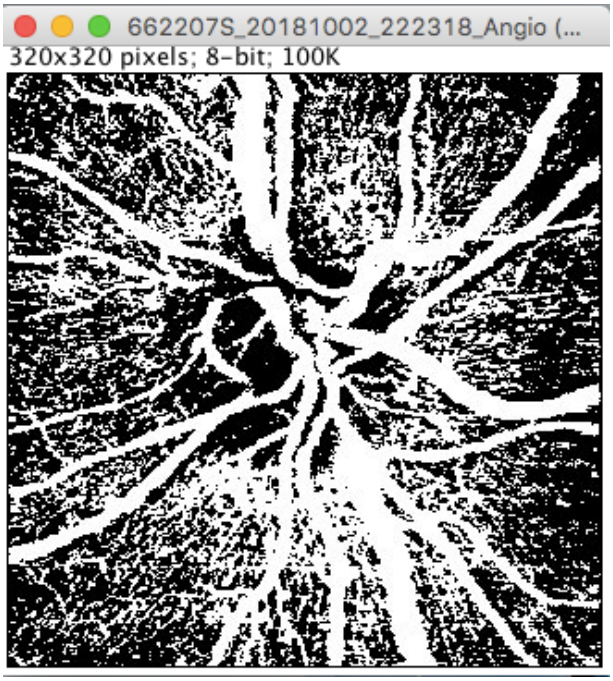
This image is a 3x3 mm scan of the ONH and peri-papillary micro vascular network, of 320x320 pixel resolution.

This image is copied onto the computer and opened in ImageJ software.

The next step is to create a mesh framework of the micro vascular grid, before vessel density analysis, to delineate/ highlight only the micro vascular network. This is done by background subtraction and then, by converting the background subtracted image into an 8 bit binary (black and white) image from the unedited RGB image. This can be done by using the 'Binary image' option under the 'Process' tab, as shown here.

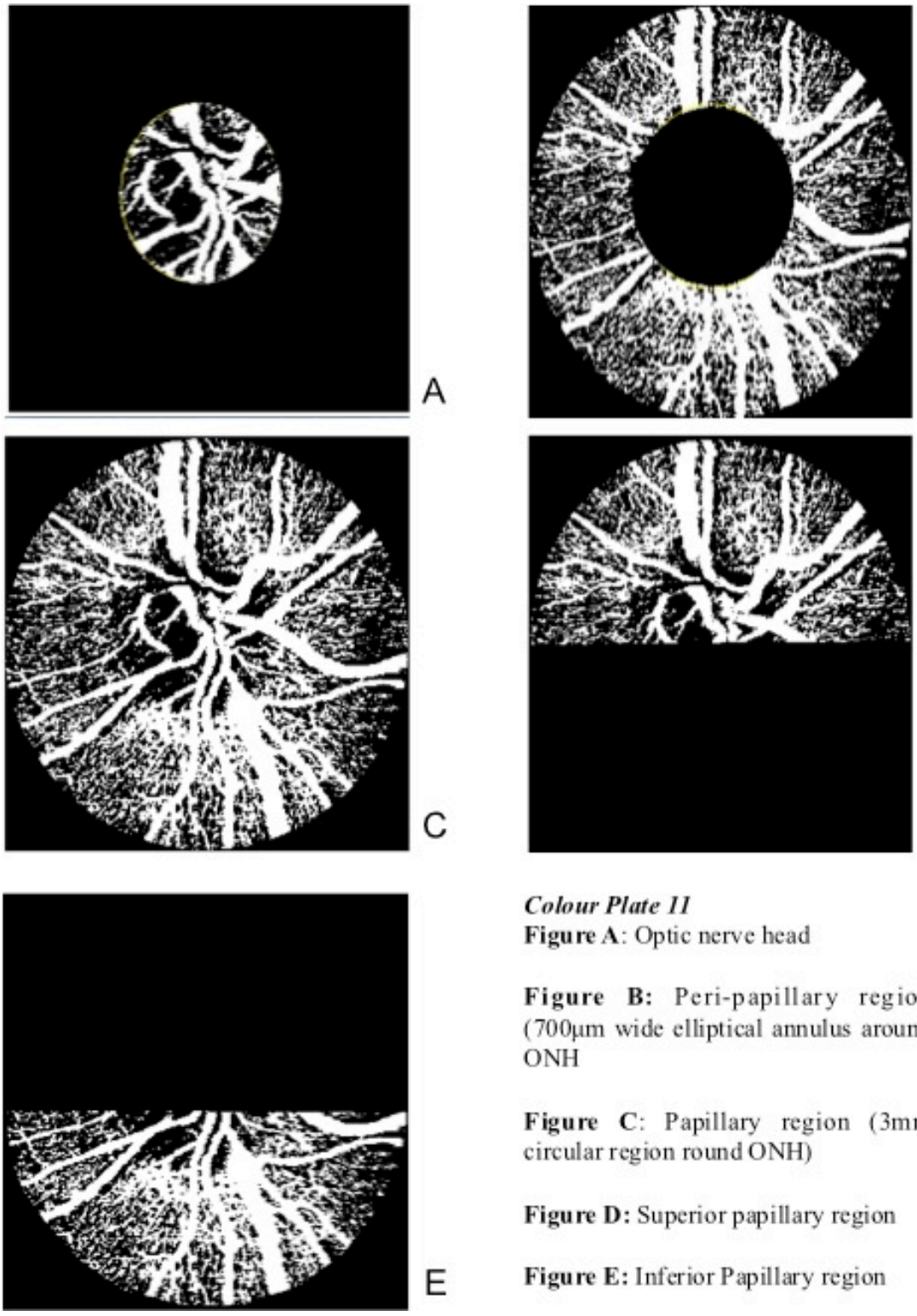


Colour Plate 9: Location of Background subtraction tab and binary map tab on toolbar in ImageJ



Colour Plate 10: Composite OCTA image, after background subtraction, conversion to binary image and preparation of micro vascular framework mesh.

Next, we start the vessel density analysis. The image is first edited by cropping out only the required areas of interest. The required area is selected using the 'Oval', 'Polygon' or the 'Free hand' selection tools in the ImageJ 'Software' tabs, after measuring the proper dimensions for the area of interest.



Colour Plate 11
Figure A: Optic nerve head

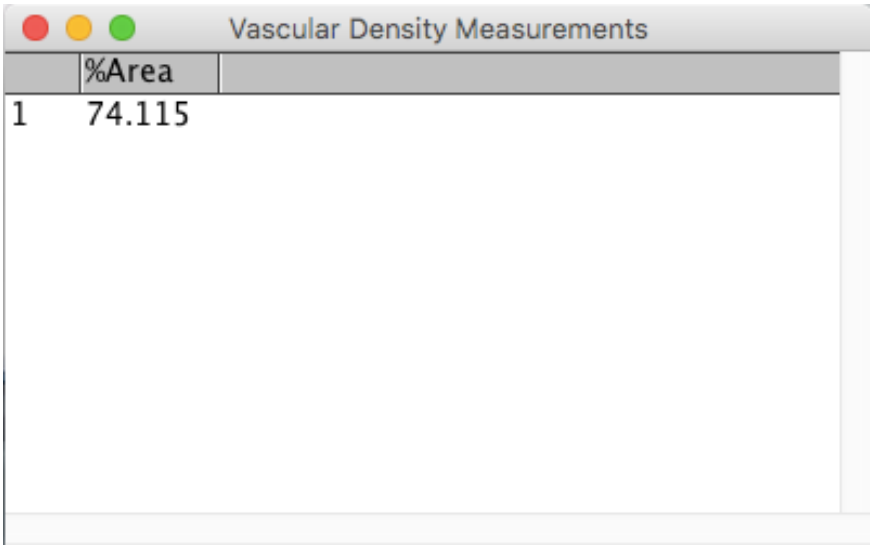
Figure B: Peri-papillary region (700µm wide elliptical annulus around ONH

Figure C: Papillary region (3mm circular region round ONH)

Figure D: Superior papillary region

Figure E: Inferior Papillary region

Then, the Vessel density in the area of interest, in each of these cropped pictures in calculated, by software analysis using ImageJ. The result is displayed as percentage area (%area)



Colour Plate 12: Window displaying the vascular density of the selected area of interest

This process is repeated for the OCT Angiography image of every selected eye, and the measurements are tabulated in Spreadsheet format by entering into Epidata.

BIAS:

- Names of patients will not be recorded in the spreadsheet for analysis – patients will be identified only with their unique identification hospital number.
- Visual acuity will be recorded as per department protocol by the respective optometrist prior to recruitment into the study
- Clinical examination of the patient and recording of findings will be done by the PI for uniformity of diagnosis

- Image analysis will be done at the end of the recruitment period or at least 2 weeks following the recruitment of the patient

SAMPLE SIZE

A sample of size 16 in each group is needed to detect 6% difference in peri-papillary vascular density between glaucoma suspects and normals (controls), with 80% power and 5% level of significance. We assume that mean and standard deviation of the peri-papillary vascular density was 86% and 92% with standard deviation of 6 and 4 respectively. We also consider an equal number in the diagnosed glaucoma group as a 3rd group for comparison.

QUANTITATIVE VARIABLES

All quantitative variables were measured as per the machine protocol and documented as raw values.

Age was considered to the nearest whole number and matching was done within ±2 years, or the measurements were statistically adjusted for age.

STATISTICAL METHODS

Data were summarized using mean (SD)/ Median (range) for continuous variables and categorical data were expressed as frequency along with percentage. The continuous variables among the groups were compared using ANOVA followed by Bonferroni as post hoc test. The categorical associations or comparisons with the three groups were performed using Chi-square test. The discriminating ability of vascular density parameters for normals compared with suspects (Ocular hypertensives); as well the suspects compared with diseased (Early POAG patients) were presented by constructing a Receiver Operating Characteristic (ROC) curve. The Area under curve (AUC) along with Standard Error (SE), Sensitivity and Specificity were reported for the optimal cut-off decided. All the analysis were performed using STATA /IC 15.0 software.

RESULTS AND ANALYSIS

A total of 54 eyes of 54 patients were studied. Table 5 shows the number of patients in each group.

Of the 54 eyes of 54 patients, 19 eyes were of the normal controls, 18 eyes were of the patients with Ocular hypertension and 17 eyes were of patients with Primary Open Angle Glaucoma.

Table 5: Distribution of patients and eyes in each group

Group	Normals	O-HTN Group	POAG Group
Number of patients (Eyes) (n)	19 (19)	18 (18)	17 (17)

O-HTN – Ocular Hypertension, POAG – Primary Open Angle Glaucoma

Of the 54 patients studied, totally, 25 (46.30%) were males and 29 (53.70%) were females. Table 6 shows the sex distribution among each of the groups studied.

Table 6: Sex distribution among the various groups

Sex	Groups			Total
	Normals	O-HTN Group	POAG Group	
Male Number (%)	6 (31.58%)	8 (44.44%)	11 (64.71%)	25 (46.30%)
Female Number (%)	13 (68.42%)	10 (55.56%)	6 (35.29%)	29 (53.70%)
Total Number (%)	19 (100%)	18 (100%)	17 (100%)	54 (100%)

O-HTN – Ocular Hypertension
POAG – Primary Open Angle Glaucoma

There was no statistically significant difference in the distribution of males and females between the three groups. ($p = 0.136$)

Of the 54 eyes of the 54 patients studied, right eyes were 26 (48.15%) and left eyes were 28 (51.85%). Table 7 shows the eye distribution among each of the groups studied.

Table 7: Distribution of right and left eye among the various groups

Eye	Groups			Total
	Normals	O-HTN Group	POAG Group	
Right Eye Number (%)	11 (57.89%)	7 (38.89%)	8 (47.06%)	26 (48.15%)
Left Eye Number (%)	8 (42.11%)	11 (61.11%)	9 (52.94%)	28 (51.85%)
Total Number (%)	19 (100.00%)	18 (100.00%)	17 (100%)	54 (100%)

O-HTN – Ocular Hypertension, POAG – Primary Open Angle Glaucoma

There was no statistically significant difference in the distribution of eyes (Right or Left) between the two groups. (p = 0.509)

Age distribution of patients in each group is seen in Table 8

Table 8: Age distribution of patients in each group Visual Field Pattern Standard Deviation

Age	Groups			p Value
	Normals	O-HTN Group	POAG Group	
Number	19	18	17	0.067
Mean Age (± SD)	48.74 (±12.10)	51.94 (± 13.33)	58.00 (± 9.33)	
Minimum to Maximum Age	30 to 68	30 to 70	42 to 70	

O-HTN – Ocular Hypertension, POAG – Primary Open Angle Glaucoma

There was no statistically significant difference in age seen among the three groups (p = 0.067). However, the patients with primary open angle glaucoma were in general, slightly older than the patients in the O-HTN and Normals group.

The Mean Ocular Perfusion Pressure (MOPP) was calculated for each patient, by measuring the BP and the IOP at the time of examination and was calculated by using the below formula: -

Mean Ocular Perfusion Pressure (MOPP) = ⅔ X [MAP – IOP]

Where, MAP = Mean Arterial Pressure; IOP = Intraocular Pressure

Mean Arterial Pressure (MAP) = DBP + (1/3)(SBP - DBP)

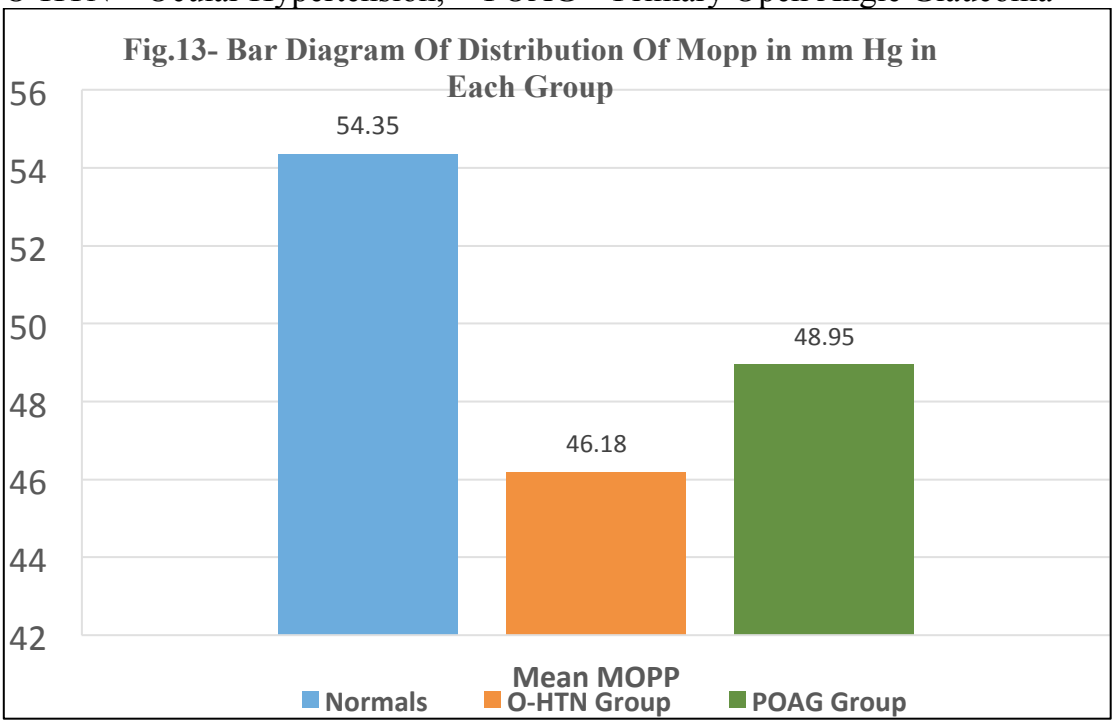
Where, SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure

The distribution of MOPP, among the groups is shown in Table 9

Table 9: Distribution of MOPP in each group

	Groups		
	Normals (n =19)	O-HTN Group (n = 18)	POAG Group (n = 17)
Mean MOPP (± SD)(Mm Hg)	54.35 (± 4.25)	46.18 (± 6.38)	48.95 (± 3.02)
Minimum to Maximum MOPP (Mm Hg)	44.88 to 63.55	33.77 to 56.00	45.77 to 56.44

O-HTN – Ocular Hypertension, POAG – Primary Open Angle Glaucoma



In our sample groups, the difference between mean MOPP in the O-HTN group and Normals was statistically significant. (8.16 mm Hg lower in O-HTN group) (p = <0.01); And the difference between the mean MOPP in the POAG group and Normals was also statistically significant. (5.40 mm Hg lower in POAG group)(p = <0.01).But the difference in mean MOPP between the O-HTN group and POAG group was not significant statistically (p = 0.278)

Out of the 54 eyes of 54 patients, a total of 19 (35.19%) patients were on Anti-glaucoma medications, majority being from the POAG group (Table 10)

Table 10: Use of Anti Glaucoma Medications in each group

	Groups		
	Normals	O-HTN Group	POAG Group
Number of patients on AGM / Total number of patients in Group (%)	0 / 19 (0%)	3 / 18 (16.67%)	16 / 17 (94.12%)

O-HTN – Ocular Hypertension, POAG – Primary Open Angle Glaucoma
AGM – Anti Glaucoma Medications

In the Vision assessment for each of the patients included in the study, Best Corrected Visual Acuity was measured from Snellen's visual acuity and was converted to LogMar visual acuity for statistical analysis. The mean LogMar visual acuity of the three groups was given in Table 11.

Table 11: Distribution of BCVA in each group

BCVA	Groups			p Value
	Normals	O-HTN Group	POAG Group	
Number	19	18	17	<0.01
Mean BCVA (± SD)	0.00 (± 0.00)	0.11 (± 0.11)	0.12 (± 0.12)	

O-HTN – Ocular Hypertension, POAG – Primary Open Angle Glaucoma
BCVA – Best Corrected Visual Acuity

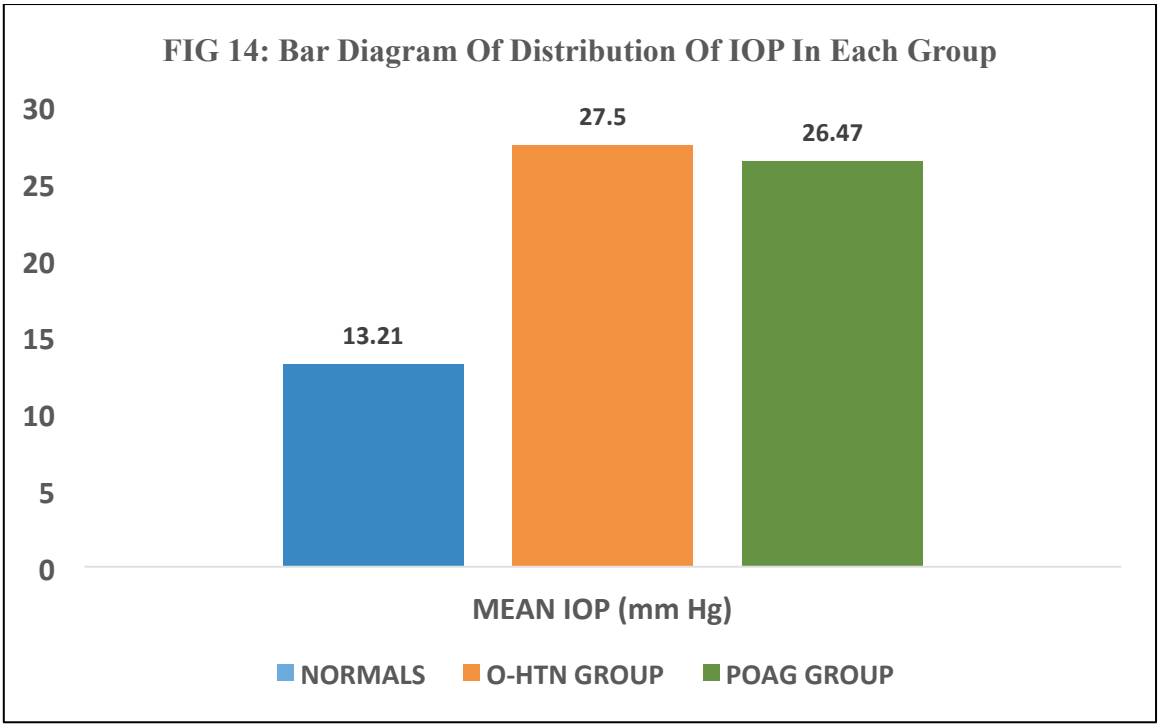
In our sample groups, the difference between mean BCVA in the O-HTN group and Normals was statistically significant (p = <0.01); and the difference between the mean BCVA in the POAG group and Normals was also statistically significant (p = <0.01). But the difference in mean BCVA between the O-HTN group and POAG group was not significant statistically (p = 1.00).

Intraocular Pressure (IOP) measured at the time of examination of the patients was analyzed and the distribution was found to be as follows (Table 12):

Table 12: Distribution of IOP in each group

IOP	Groups			p Value
	Normals (n = 19)	O-HTN Group (n = 18)	POAG Group (n = 17)	
Mean IOP (Mm Hg) (± SD)	13.21 (± 2.27)	27.50 (± 3.70)	26.47 (± 2.90)	<0.01
Minimum to Maximum IOP (Mm Hg)	08 to 16	24 to 36	22 to 32	

O-HTN – Ocular Hypertension, POAG – Primary Open Angle Glaucoma
IOP - Intraocular Pressure



In our sample groups, the difference between mean IOP in the O-HTN group and Normals was statistically significant (p = <0.01); and the difference between the mean IOP in the POAG group and Normals was also statistically significant (p = <0.01).But the difference in mean IOP between the O-HTN group and POAG group was not significant statistically (p = 0.947)

Differences in the Vertical disc diameter (VDD) and Cup: Disc Ratio (CDR) between the groups was also measured and the results are as follows (Table 13 and 14):

Table 13: Distribution of VDD in each group

	Groups			p Value
	Normals (n = 19)	O-HTN Group (n = 18)	POAG Group (n = 17)	
Mean VDD (mm) (± SD)	1.96 (± 0.19)	1.91 (± 0.14)	1.95 (± 0.23)	0.714
Minimum to Maximum VDD(mm)	1.65 to 2.34	1.69 to 2.21	1.65 to 2.47	

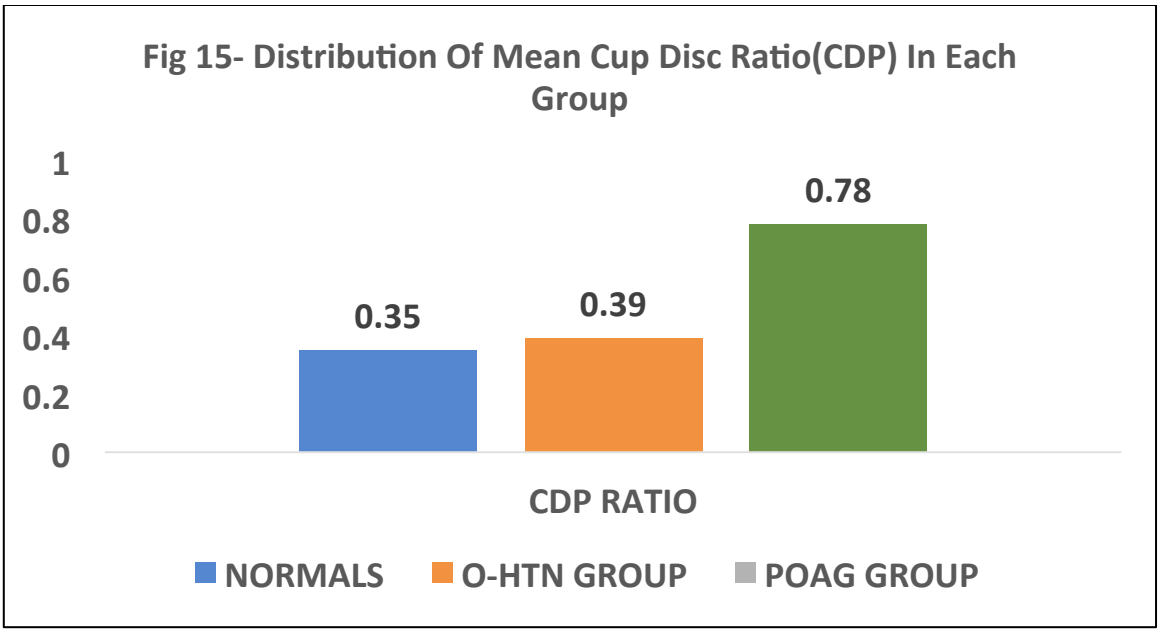
O-HTN – Ocular Hypertension, POAG – Primary Open Angle Glaucoma
VDD – Vertical Disc Diameter

There was no statistically significant difference in the Vertical Disc Diameter between the three groups. (p = 0.714)

Table 14: Distribution of CDR in each group

	Groups			p Value
	Normals (n = 19)	O-HTN Group (n = 18)	POAG Group (n = 17)	
Mean CDR (± SD)	0.35 (± 0.10)	0.39 (± 0.14)	0.74 (± 0.07)	<0.01
Minimum to Maximum CDR	0.10 to 0.50	0.20 to 0.70	0.60 to 0.80	

O-HTN – Ocular Hypertension, POAG – Primary Open Angle Glaucoma, CDR – Cup: Disc Ratio



There was a statistically significant difference in the Cup: Disc Ratio (CDR) between the Normals and POAG group (p = <0.01) and also a statistically significant difference between the O-HTN Group and POAG group (p = <0.01)

But there was no statistically significant difference in the CDR between Normals and O-HTN Group. (p = 0.754)

The Automated Perimetry testing by Humphrey Field Analyzer, done for all the 54 patients included in the study. The machine calculation of the Mean Deviation (MD)

and Pattern Standard Deviation (PSD) for each eye tested, was analyzed. The results are as follows (Table 15): -

Table 15: Distribution of Visual Field Mean Deviation (MD) and Pattern Standard Deviation (PSD) in each group

	Groups			p Value
	Normals (n = 19)	O-HTN Group (n = 18)	POAG Group (n = 17)	
Mean MD (± SD)(in dB)	- 4.82 (± 1.85)	- 4.48 (± 1.72)	- 8.39 (± 1.58)	<0.01
Mean PSD (± SD)(in dB)	1.87 (± 0.74)	2.69 (± 1.72)	4.85 (± 2.59)	<0.01

O-HTN – Ocular Hypertension, POAG – Primary Open Angle Glaucoma
MD - Visual Field Mean Deviation, PSD - Visual Field Pattern Standard Deviation

There was a statistically significant difference in the Visual Field Mean Deviation (MD) between the Normals and POAG group (p = <0.01) and also a statistically significant difference between the O-HTN Group and POAG group (p = <0.01). But there was no statistically significant difference in the Visual Field Mean Deviation (MD) between Normals and O-HTN Group. (p = 1.00)

When comparing the Visual Field Pattern Standard Deviation (PSD), there was a statistically significant difference between the Normals and POAG group (p = <0.01) and also a statistically significant difference between the O-HTN Group and POAG group (p = <0.01). But there was no statistically significant difference in the Visual Field Pattern Standard Deviation (PSD) between Normals and O-HTN Group. (p = 0.521)

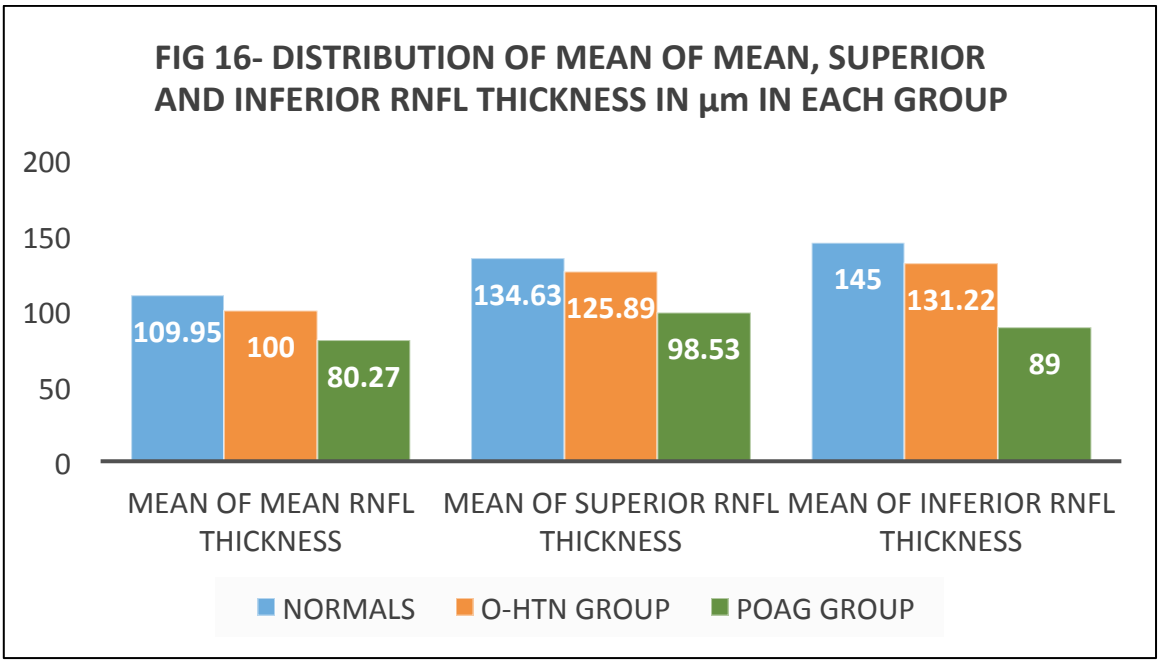
Next, the Retinal Nerve Fiber Layer Thickness (RNFL Thickness), measured by Optical Coherence Tomography (OCT), was analyzed. The measurements were recorded as Mean RNFL Thickness, and also separately as

Superior and Inferior RNFL Thickness. The analysis showed the following results (Table 16): -

Table 16: - Distribution of Mean, Superior and Inferior RNFL Thickness in each group

RNFL Thickness	Groups			p Value
	Normals (n = 19)	O-HTN Group (n = 18)	POAG Group (n = 17)	
Mean of Mean RNFL Thickness (± SD)(µm)	109.95 (± 11.05)	100.00 (± 13.02)	80.27 (± 13.52)	<0.01
Mean of Superior RNFL Thickness (± SD)(µm)	134.63 (± 21.74)	125.89 (± 18.71)	98.53 (± 26.26)	<0.01
Mean of Inferior RNFL Thickness (± SD)(µm)	145.00 (± 14.76)	131.22 (± 16.15)	89.00 (± 13.22)	<0.01

O-HTN – Ocular Hypertension, POAG – Primary Open Angle Glaucoma
RNFL – Retinal Nerve Fiber Layer



There was a statistically significant difference in the Mean RNFL Thickness between the Normals and POAG group (p = <0.01) and also a statistically significant difference between the O-HTN Group and POAG group (p = <0.01). But there was no

statistically significant difference in the Mean RNFL Thickness between Normals and O-HTN Group. (p = 0.06)

When comparing the Superior RNFL Thickness, there was a statistically significant difference between the Normals and POAG group (p = <0.01) and also a statistically significant difference between the O-HTN Group and POAG group (p = <0.01). But there was no statistically significant difference in the Superior RNFL Thickness between Normals and O-HTN Group. (p = 0.720).

When comparing the Inferior RNFL Thickness, there was a statistically significant difference between the Normals and POAG group (p = <0.01) and also a statistically significant difference between the O-HTN Group and POAG group (p = <0.01)

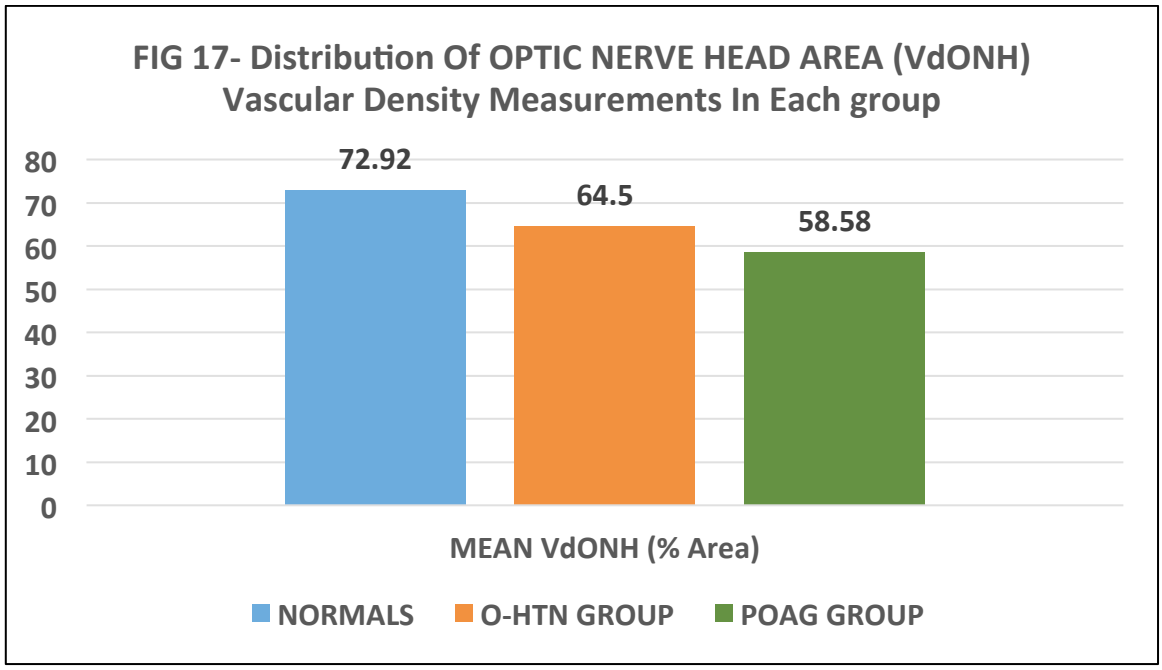
An important difference noted was that there was a statistically significant difference in the Inferior RNFL Thickness between the Normals and O-HTN Group. (p = 0.020).

Finally, the Vascular density measurement was done by analysis of the Optical Coherence Tomography Angiography images of the Optic Nerve Head and Papillary area; and the entire image was divided and analysis was done in the Optic Nerve Head area (VdONH), Peri-papillary area (VdPPA), Papillary area (VdPA), Superior Papillary (VdSPA) and Inferior Papillary (VdIPA) areas. The results were as follows: -

Table 17: Distribution of Optic Nerve Head area (VdONH) Vascular Density measurements in each group

VdONH	Groups			p Value
	Normals (n = 19)	O-HTN Group (n = 18)	POAG Group (n = 17)	
Mean VdONH (± SD)(%Area)	72.92 (± 2.44)	64.50 (± 3.41)	58.58 (± 2.46)	<0.01
Minimum to Maximum VdONH(%Area)	66.70 to 77.29	57.49 to 68.94	54.08 to 61.95	

O-HTN – Ocular Hypertension, POAG – Primary Open Angle Glaucoma
VdONH - Optic Nerve Head area Vascular Density measurements



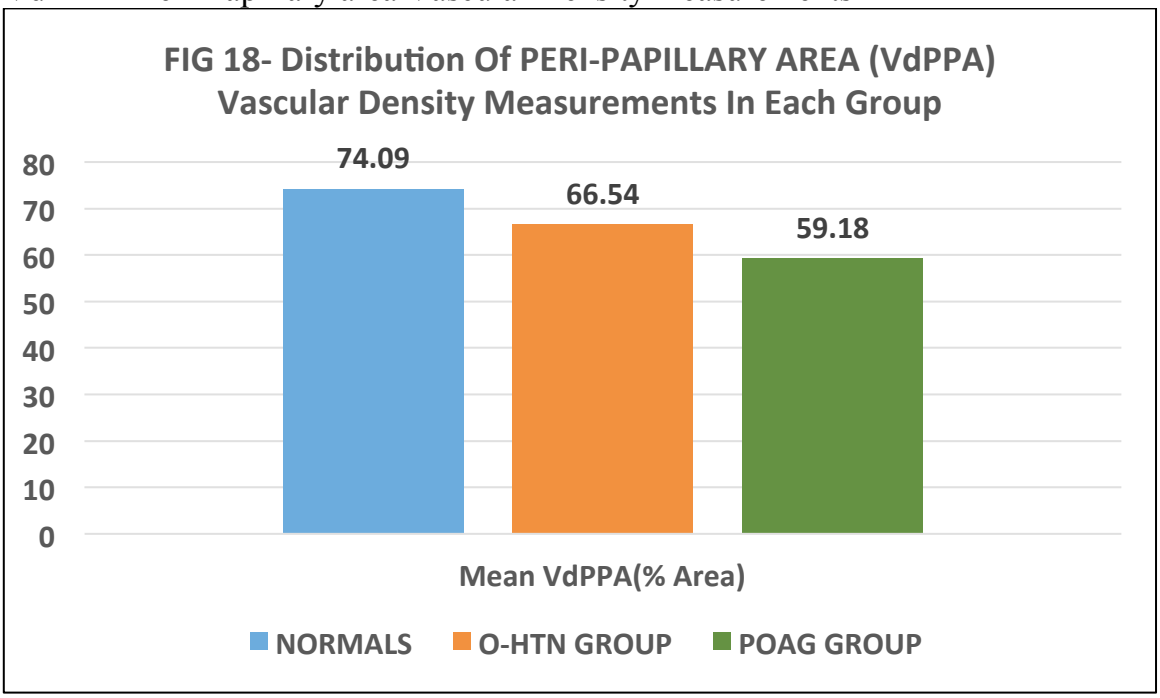
There was a statistically significant difference in the Optic Nerve Head area (VdONH) Vascular Density measurements between the Normals and POAG group (p = <0.01), also a statistically significant difference between the O-HTN Group and POAG group (p = <0.01) and also a statistically significant difference between the Normals and O-HTN group (p = <0.01)

The VdONH measurements, in the descending order of percentage area of Vascular density, were, Normals > O-HTN > POAG Group (in that order) and the difference was statistically significant between all three groups. (P = <0.01)

Table 18: Distribution of Peri-Papillary area (VdPPA) Vascular Density measurements in each group

VdPPA	Groups			p Value
	Normals (n = 19)	O-HTN Group (n = 18)	POAG Group (n = 17)	
Mean VdPPA (± SD)(%Area)	74.09 (± 2.03)	66.54 (± 1.48)	59.18 (± 2.57)	<0.01
Minimum to Maximum VdPPA (%Area)	69.01 to 78.48	63.06 to 68.90	54.68 to 63.32	

O-HTN – Ocular Hypertension, POAG – Primary Open Angle Glaucoma
VdPPA - Peri-Papillary area Vascular Density measurements



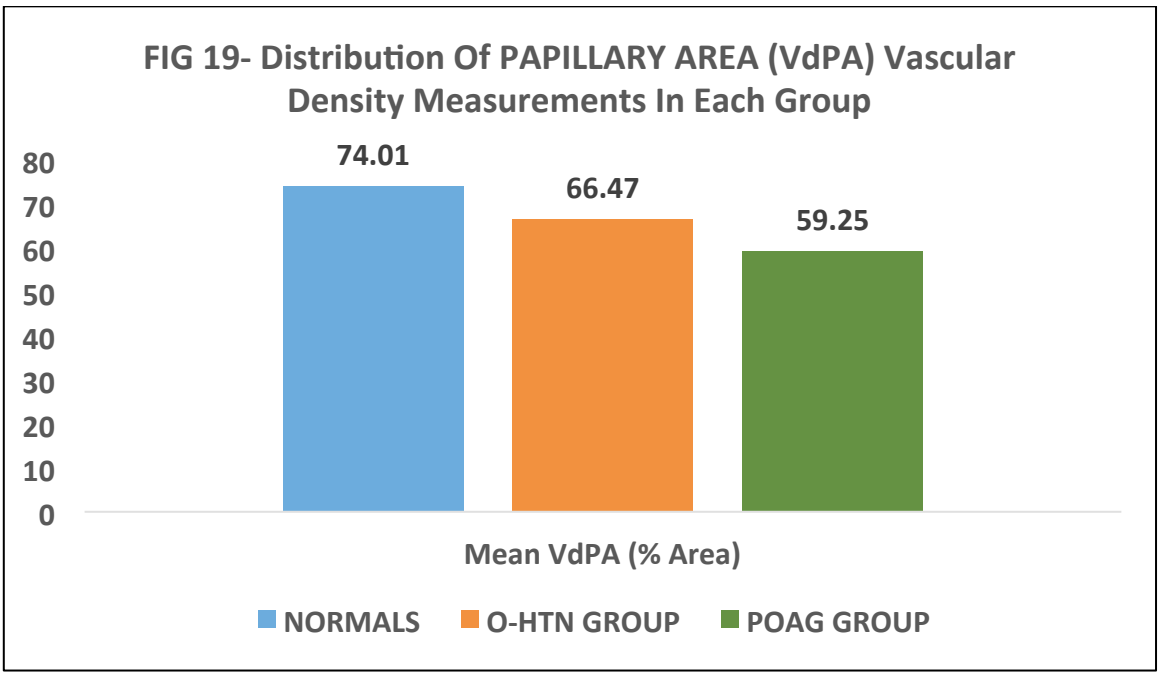
There was a statistically significant difference in the Peri-Papillary area (VdPPA) Vascular Density measurements between the Normals and POAG group (p = <0.01), also a statistically significant difference between the O-HTN Group and POAG group (p = <0.01) and also a statistically significant difference between the Normals and O-HTN group (p = <0.01)

The VdPPA measurements, in the descending order of percentage area of Vascular density, were, Normals > O-HTN > POAG Group (in that order) and the difference was statistically significant between all three groups. (P = <0.01)

Table 19: Distribution of Papillary area (VdPA) Vascular Density measurements in each group

VdPA	Groups			p Value
	Normals (n = 19)	O-HTN Group (n = 18)	POAG Group (n = 17)	
Mean VdPA (± SD)(%Area)	74.01 (± 1.45)	66.47 (± 2.26)	59.25 (± 2.33)	<0.01
Minimum to Maximum VdPA(%Area)	71.42 to 76.87	60.09 to 69.72	55.22 to 63.02	

O-HTN – Ocular Hypertension, POAG – Primary Open Angle Glaucoma
VdPA - Papillary area Vascular Density measurements



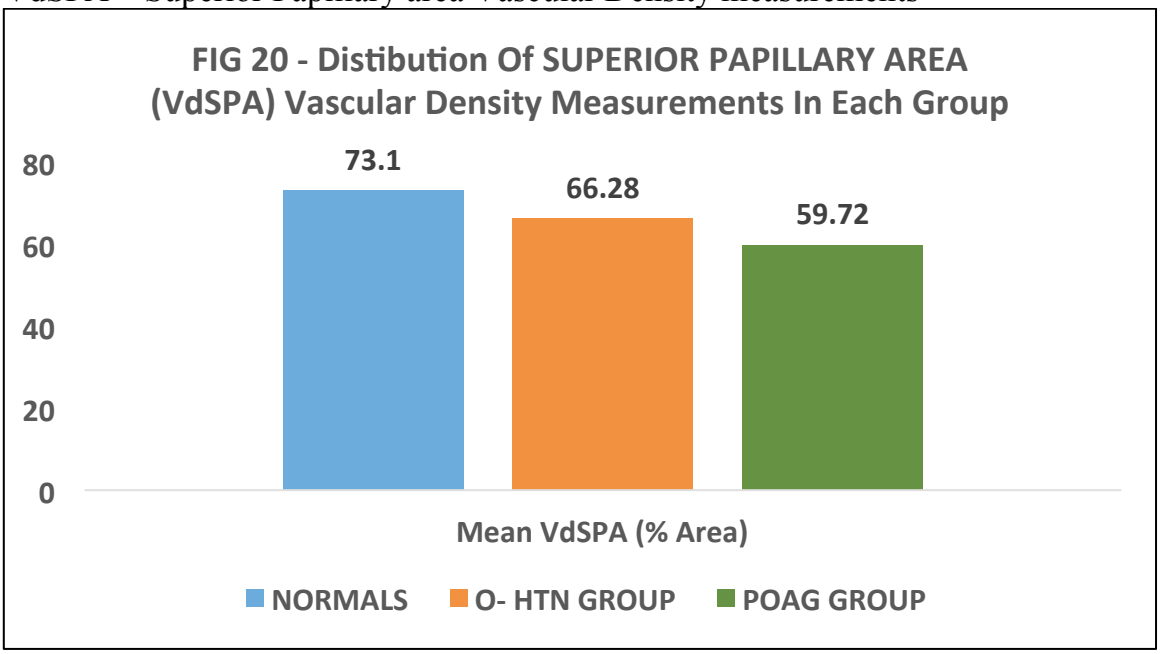
There was a statistically significant difference in the Papillary area (VdPA) Vascular Density measurements between the Normals and POAG group (p = <0.01), also a statistically significant difference between the O-HTN Group and POAG group (p = <0.01) and also a statistically significant difference between the Normals and O-HTN group (p = <0.01)

The VdPA measurements, in the descending order of percentage area of Vascular density, were, Normals > O-HTN > POAG Group (in that order) and the difference was statistically significant between all three groups. (P = <0.01)

Table 20: Distribution of Superior Papillary area (VdSPA) Vascular Density measurements in each group

VdSPA	Groups			p Value
	Normals (n = 19)	O-HTN Group (n = 18)	POAG Group (n = 17)	
Mean VdSPA (± SD)(%Area)	73.10 (± 2.45)	66.28 (± 2.87)	59.72 (± 1.75)	<0.01
Minimum to Maximum VdSPA(%Area)	68.29 to 78.11	58.73 to 69.73	56.31 to 62.53	

O-HTN – Ocular Hypertension, POAG – Primary Open Angle Glaucoma
VdSPA – Superior Papillary area Vascular Density measurements



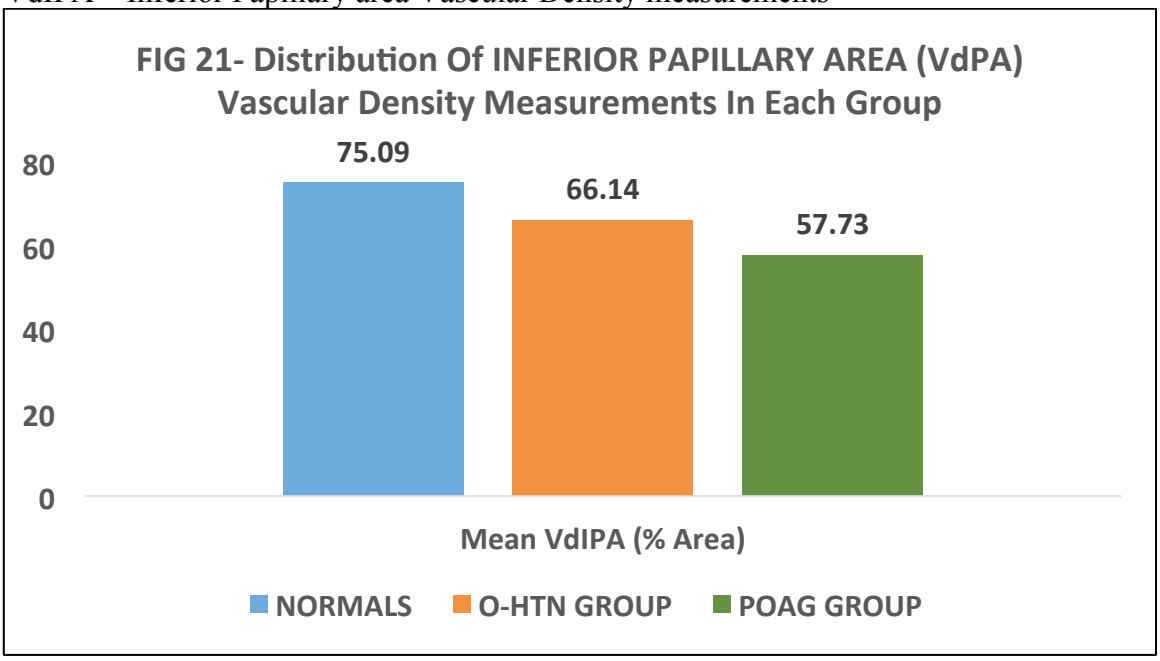
There was a statistically significant difference in the Superior Papillary area (VdSPA) Vascular Density measurements between the Normals and POAG group (p = <0.01), also a statistically significant difference between the O-HTN Group and POAG group (p = <0.01) and also a statistically significant difference between the Normals and O-HTN group (p = <0.01).

The VdSPA measurements, in the descending order of percentage area of Vascular density, were, Normals > O-HTN > POAG Group (in that order) and the difference was statistically significant between all three groups. (P = <0.01)

Table 21: Distribution of Inferior Papillary area (VdIPA) Vascular Density measurements in each group

VdIPA	Groups			p Value
	Normals (n = 19)	O-HTN Group (n = 18)	POAG Group (n = 17)	
Mean VdIPA (± SD)(%Area)	75.09 (± 1.76)	66.14 (± 2.19)	57.73 (± 2.34)	<0.01
Minimum to Maximum VdIPA(%Area)	72.42 to 77.85	61.67 to 70.58	53.53 to 61.98	

O-HTN – Ocular Hypertension, POAG – Primary Open Angle Glaucoma
VdIPA – Inferior Papillary area Vascular Density measurements



There was a statistically significant difference in the Inferior Papillary area (VdIPA) Vascular Density measurements between the Normals and POAG group (p = <0.01), also a statistically significant difference between the O-HTN Group and POAG group (p = <0.01) and also a statistically significant difference between the Normals and O-HTN group (p = <0.01)

The VdIPA measurements, in the descending order of percentage area of Vascular density, were, Normals > O-HTN > POAG Group (in that order) and the difference was statistically significant between all three groups. (P = <0.01)

Next, for each of the areas of interest analyzed for Vascular density measurements, based on the distribution of above results, Receiver Operating Characteristic (ROC) Curves were constructed by plotting the True positive fraction (TPF) (Sensitivity) on the Y-Axis and False positive fraction (FPF) (1-Sensitivity) on the X – Axis. The sensitivities and specificities at each point along the curve were determined and the Cut-offs for each parameter, to differentiate between the two groups being compared, was determined based on the combination of maximum sensitivity and specificity. The ROC curve was described by its components; Area under the curve (AUC), Sensitivity at specified specificity and Partial Area under the curve.

Firstly, The O-HTN Group was compared with the Normal Group, to determine the cut-off point, at each of the areas of interest.

ROC Curve 1: ROC Curve of Optic Nerve Head area (VdONH) Vascular Density measurements (O-HTN Group Vs. Normals)

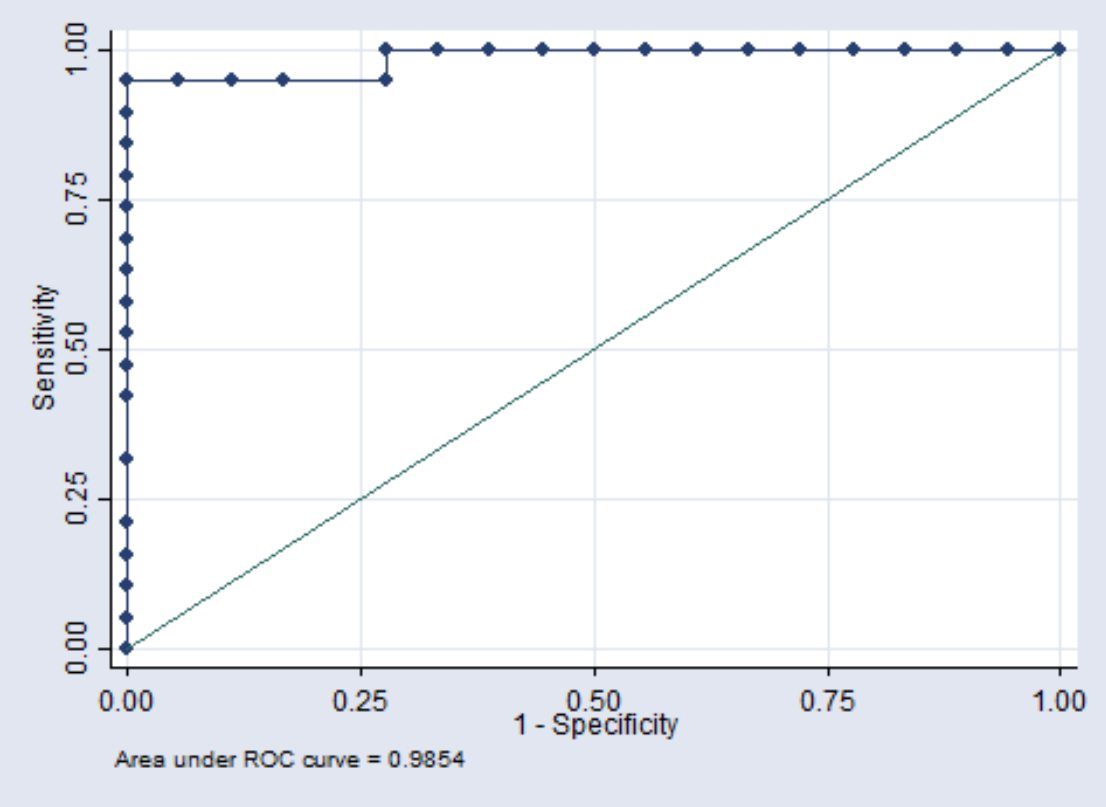


Table 22: Cut-off value for differentiating between O-HTN group and Normals using ONH Vascular density measurements (VdONH)

VdONH	O-HTN group Vs. Normals (95% Confidence Interval) (n = 37)			
	AUC (SE)	CUT-OFF (%)	SENSITIVITY	SPECIFICITY
	0.9854 (0.0157)	> 69.73%	100.00%	94.74%

VdONH - Optic Nerve Head area Vascular Density measurements
O-HTN – Ocular Hypertension, AUC – Area under Curve
SE – Standard Error

Therefore a VdONH Vascular Density measurement above 69.73% suggests likely to be Normal and below suggests likely to be O-HTN.

ROC Curve 2: ROC Curve of Peri-Papillary area (VdPPA) Vascular Density measurements (O-HTN Group Vs. Normals)

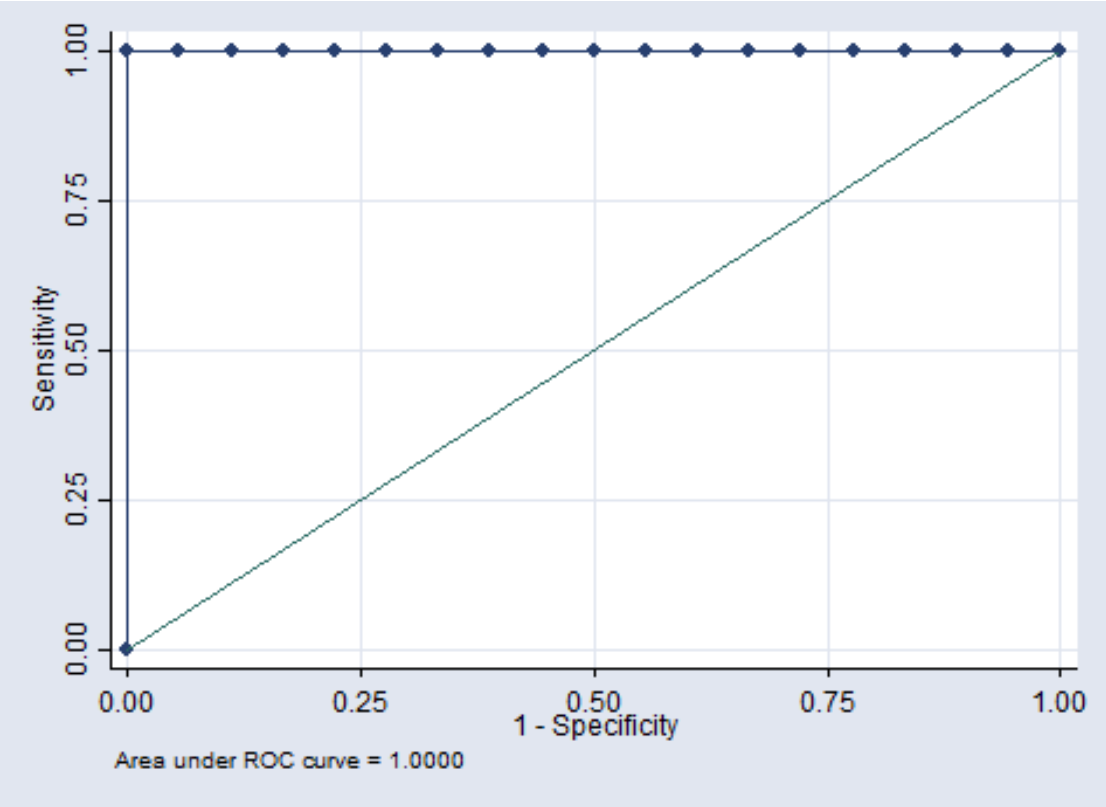


Table 23: Cut-off value for differentiating between O-HTN group and Normals using Peri-Papillary Vascular density measurements (VdPPA)

VdPPA	O-HTN group Vs. Normals (95% Confidence Interval) (n = 37)			
	AUC (SE)	CUT-OFF (%)	SENSITIVITY	SPECIFICITY
	1.000 (0.000)	> 69.01%	100.00%	100.00%

VdPPA – Peri-Papillary area Vascular Density measurements
O-HTN – Ocular Hypertension
AUC – Area under Curve, SE – Standard Error

Therefore a VdPPA Vascular Density measurement above 69.01% suggests likely to be Normal and below suggests likely to be O-HTN.

ROC Curve 3: ROC Curve of Papillary area (VdPA) Vascular Density measurements (O-HTN Group Vs. Normals)

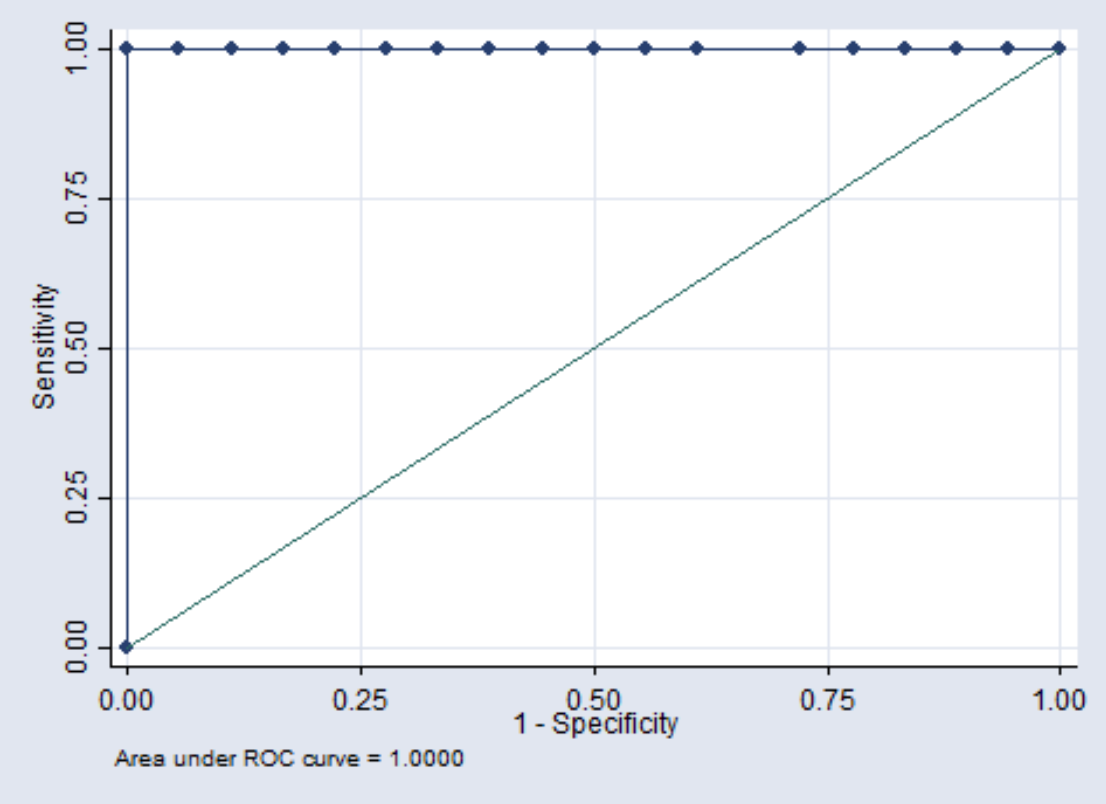


Table 24: Cut-off value for differentiating between O-HTN group and Normals using Papillary Vascular density measurements (VdPA)

VdPA	O-HTN group Vs. Normals (95% Confidence Interval) (n = 37)			
	AUC (SE)	CUT-OFF (%)	SENSITIVITY	SPECIFICITY
	1.000 (0.000)	> 71.42%	100.00%	100.00%

VdPA – Papillary area Vascular Density measurements
O-HTN – Ocular Hypertension
AUC – Area under Curve
SE – Standard Error

Therefore a VdPA Vascular Density measurement above 71.42% suggests likely to be Normal and below suggests likely to be O-HTN.

ROC Curve 4: ROC Curve of Superior Papillary area (VdSPA) Vascular Density measurements (O-HTN Group Vs. Normals)

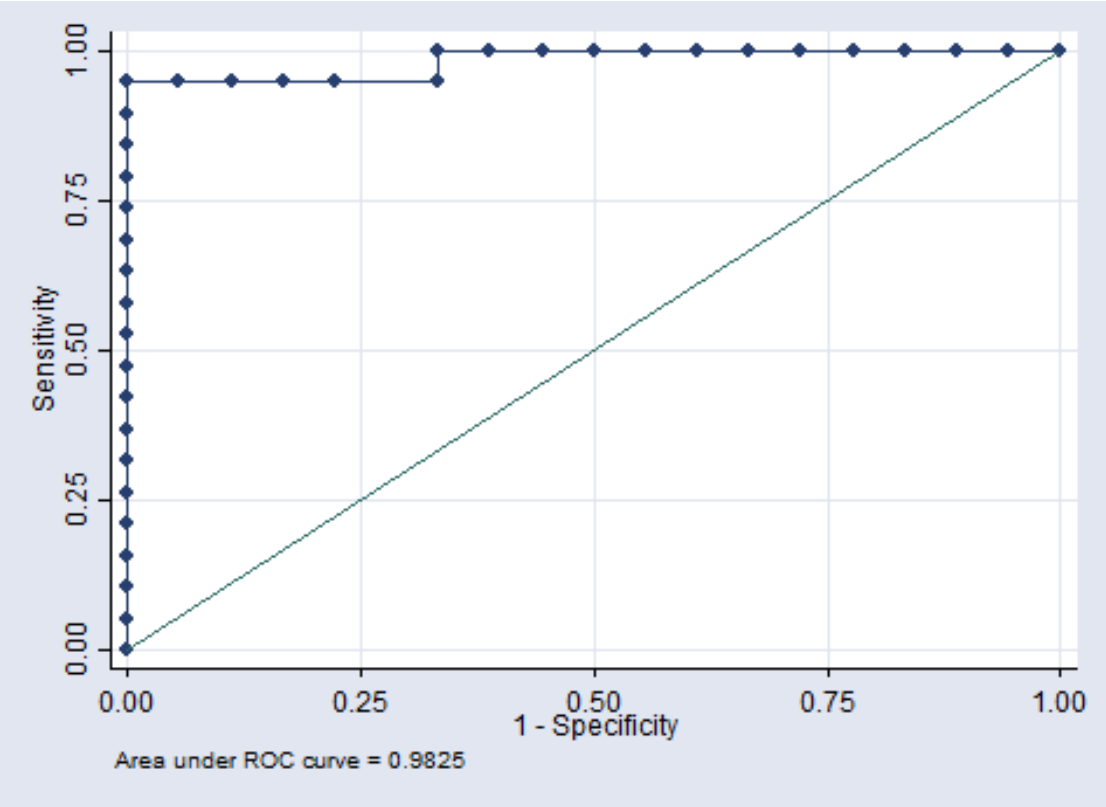


Table 25: Cut-off value for differentiating between O-HTN group and Normals using Superior Papillary Vascular density measurements (VdSPA)

VdSPA	O-HTN group Vs. Normals (95% Confidence Interval) (n = 37)			
	AUC (SE)	CUT-OFF (%)	SENSITIVITY	SPECIFICITY
	0.9825 (0.0185)	> 70.03%	100.00%	94.74%

VdSPA – Superior Papillary area Vascular Density measurements
O-HTN – Ocular Hypertension
AUC – Area under Curve, SE – Standard Error

Therefore a VdSPA Vascular Density measurement above 70.03% suggests likely to be Normal and below suggests likely to be O-HTN.

ROC Curve 5: ROC Curve of Inferior Papillary area (VdIPA) Vascular Density measurements (O-HTN Group Vs. Normals)

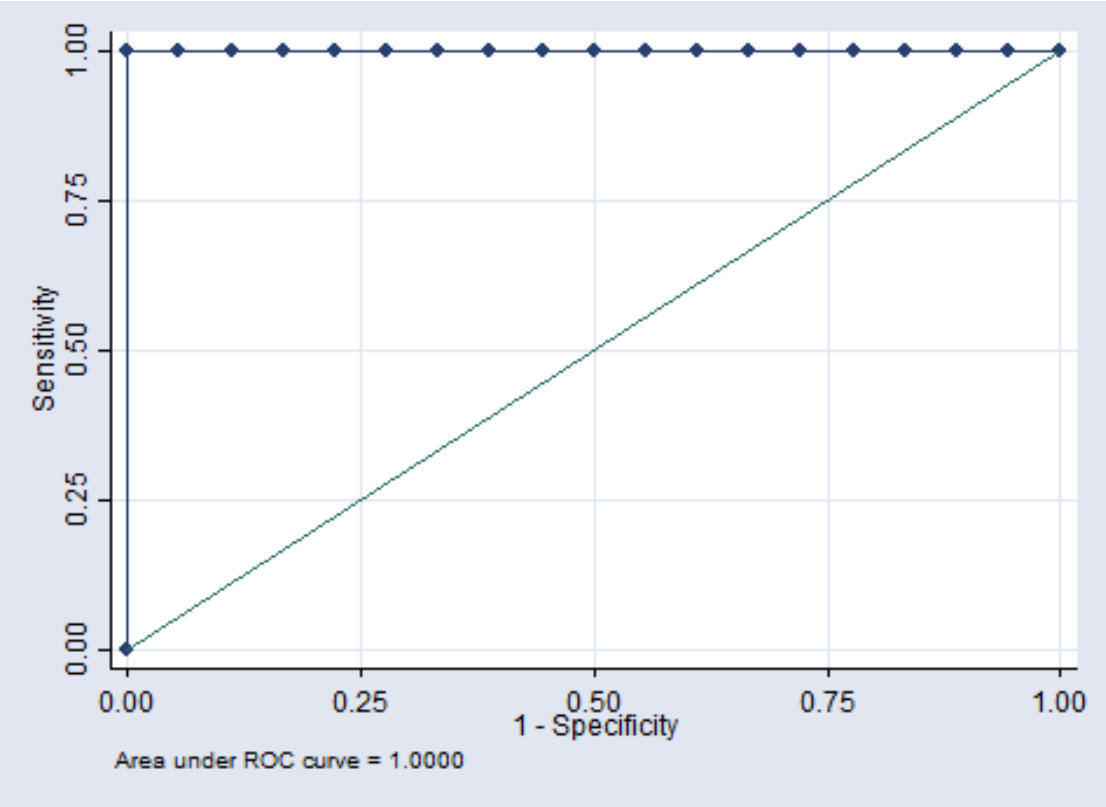


Table 26: Cut-off value for differentiating between O-HTN group and Normals using Inferior Papillary Vascular density measurements (VdIPA)

VdIPA	O-HTN group Vs. Normals (95% Confidence Interval) (n = 37)			
	AUC (SE)	CUT-OFF (%)	SENSITIVITY	SPECIFICITY
	1.0000 (0.0000)	> 72.42%	100.00%	100.00%

VdIPA – Inferior Papillary area Vascular Density measurements
O-HTN – Ocular Hypertension
AUC – Area under Curve, SE – Standard Error

Therefore a VdIPA Vascular Density measurement above 72.42% suggests likely to be Normal and below suggests likely to be O-HTN.

Next, the O-HTN Group was compared with the POAG Group, to determine the cut-off point, at each of the areas of interest.

ROC Curve 6: ROC Curve of Optic Nerve Head area (VdONH) Vascular Density measurements (O-HTN Group Vs. POAG Group)

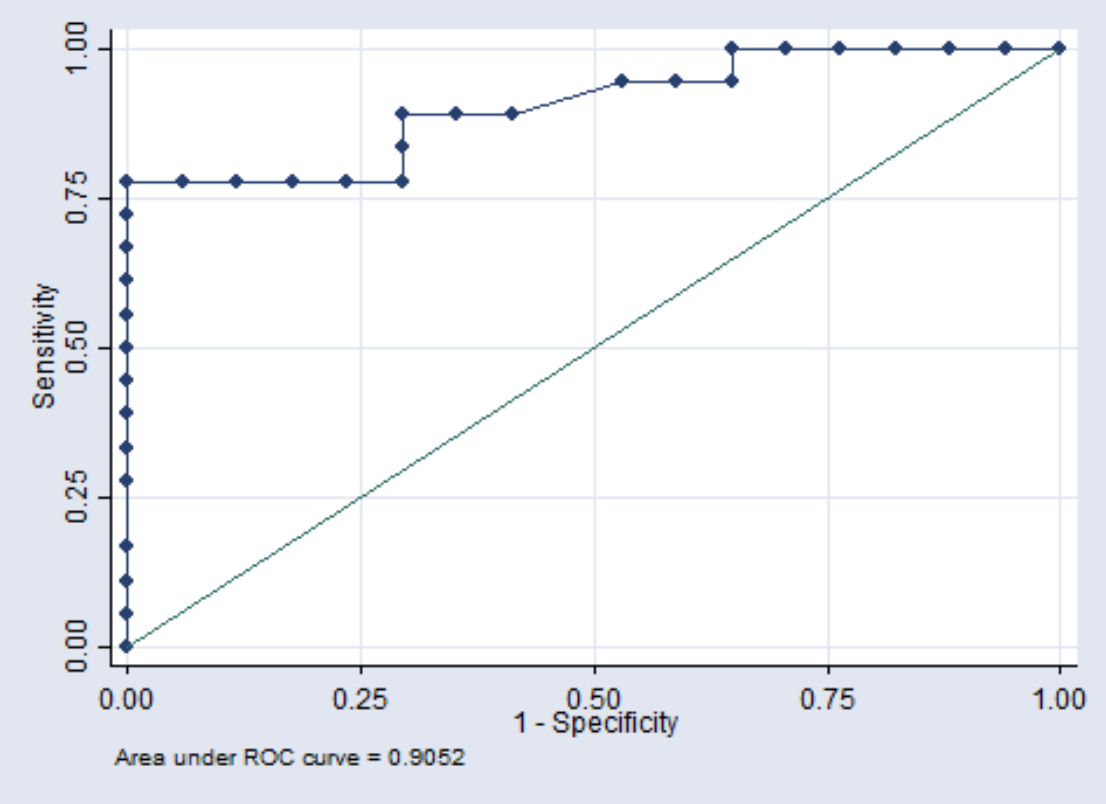


Table 27: Cut-off value for differentiating between O-HTN group and POAG Group using ONH Vascular density measurements (VdONH)

VdONH	O-HTN group Vs. POAG group (95% Confidence Interval) (n = 35)			
	AUC (SE)	CUT-OFF (%)	SENSITIVITY	SPECIFICITY
	0.9052 (0.0514)	> 62.65%	100.00%	77.78%

VdONH - Optic Nerve Head area Vascular Density measurements
O-HTN – Ocular Hypertension, POAG – Primary Open Angle Glaucoma
AUC – Area under Curve, SE – Standard Error

Therefore a VdONH Vascular Density measurement above 62.65% suggests likely to be O-HTN and below suggests likely to be POAG.

ROC Curve 7: ROC Curve of Peri-Papillary area (VdPPA) Vascular Density measurements (O-HTN Group Vs. POAG Group)

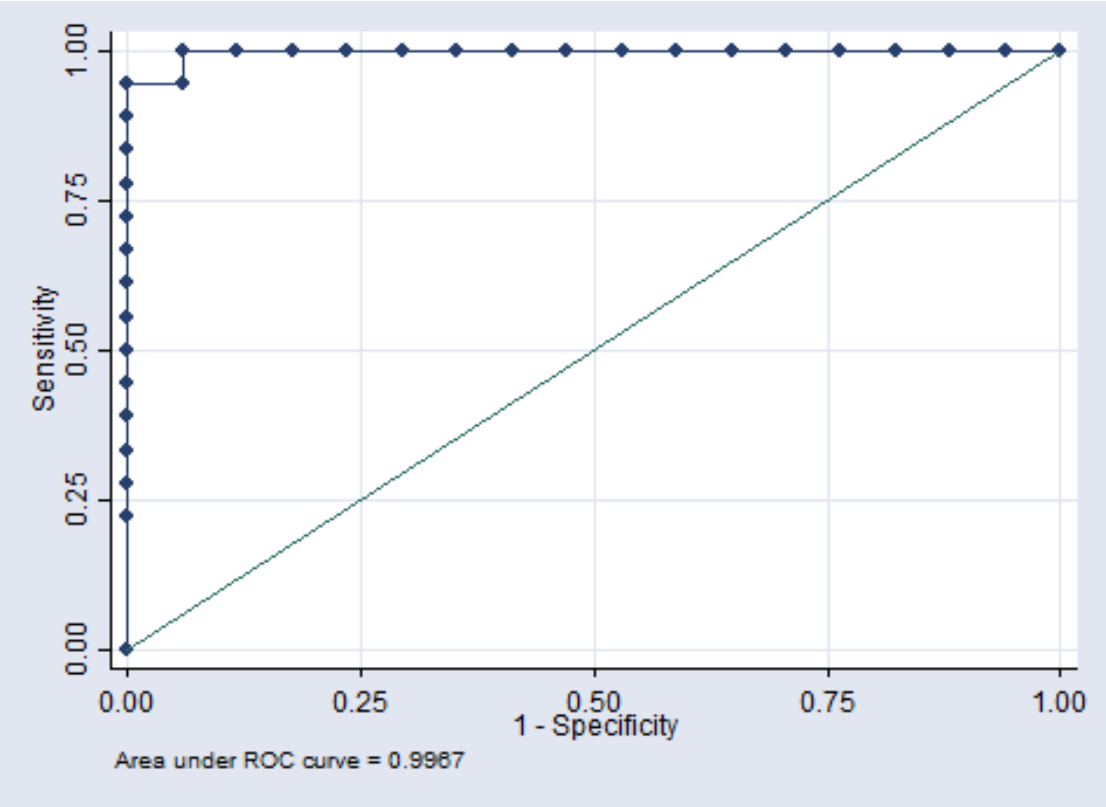


Table 28: Cut-off value for differentiating between O-HTN group and POAG Group using Peri-Papillary area (VdPPA) Vascular Density measurements

VdPPA	O-HTN group Vs. POAG group (95% Confidence Interval) (n = 35)			
	AUC (SE)	CUT-OFF (%)	SENSITIVITY	SPECIFICITY
	0.9967 (0.0046)	> 64.86 %	100.00%	94.44%

VdPPA - Peri-Papillary area Vascular Density measurements
O-HTN – Ocular Hypertension, POAG – Primary Open Angle Glaucoma
AUC – Area under Curve, SE – Standard Error

Therefore a VdPPA Vascular Density measurement above 64.86% suggests likely to be O-HTN and below suggests likely to be POAG.

ROC Curve 8: ROC Curve of Papillary area (VdPA) Vascular Density measurements (O-HTN Group Vs. POAG Group)

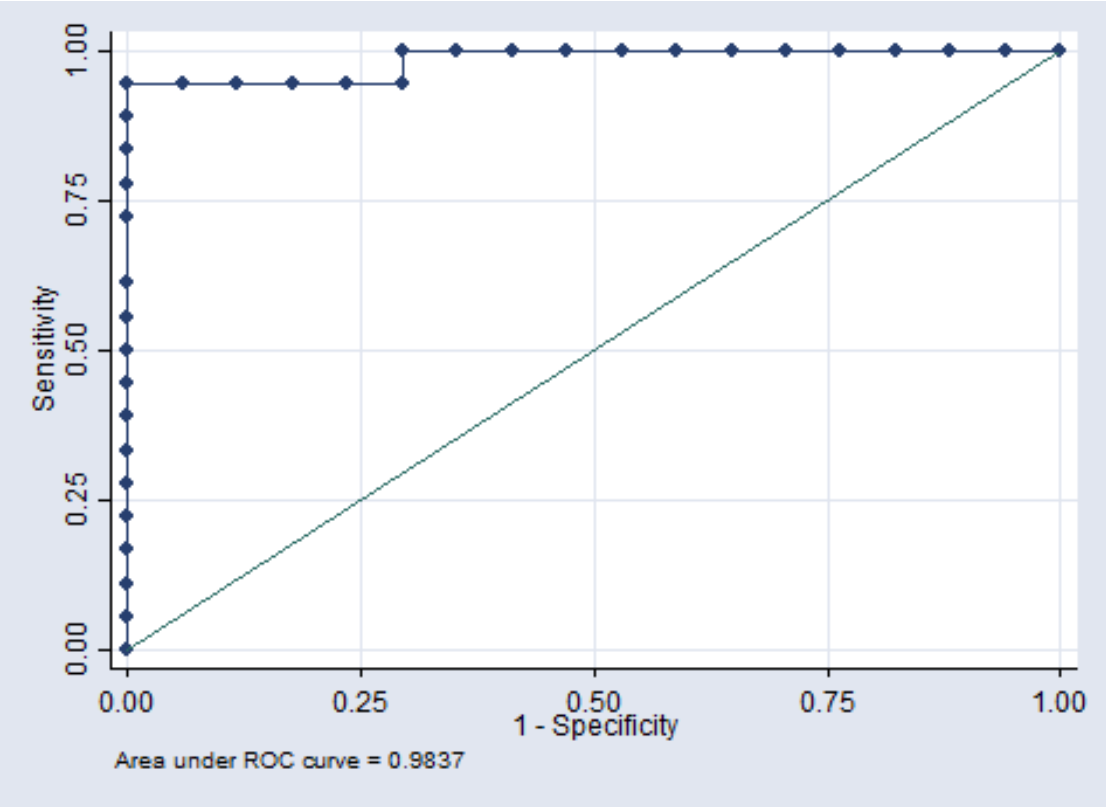


Table 29: Cut-off value for differentiating between O-HTN group and POAG Group using Papillary area (VdPA) Vascular Density measurements

VdPA	O-HTN group Vs. POAG group (95% Confidence Interval) (n = 35)			
	AUC (SE)	CUT-OFF (%)	SENSITIVITY	SPECIFICITY
	0.9837 (0.0175)	> 63.07 %	100.00%	94.44%

VdPA - Papillary area Vascular Density measurements
O-HTN – Ocular Hypertension
POAG – Primary Open Angle Glaucoma
AUC – Area under Curve, SE – Standard Error

Therefore a VdPA Vascular Density measurement above 63.07 % suggests

likely to be O-HTN and below suggests likely to be POAG

ROC Curve 9: ROC Curve of Superior Papillary area (VdSPA) Vascular Density measurements (O-HTN Group Vs. POAG Group)

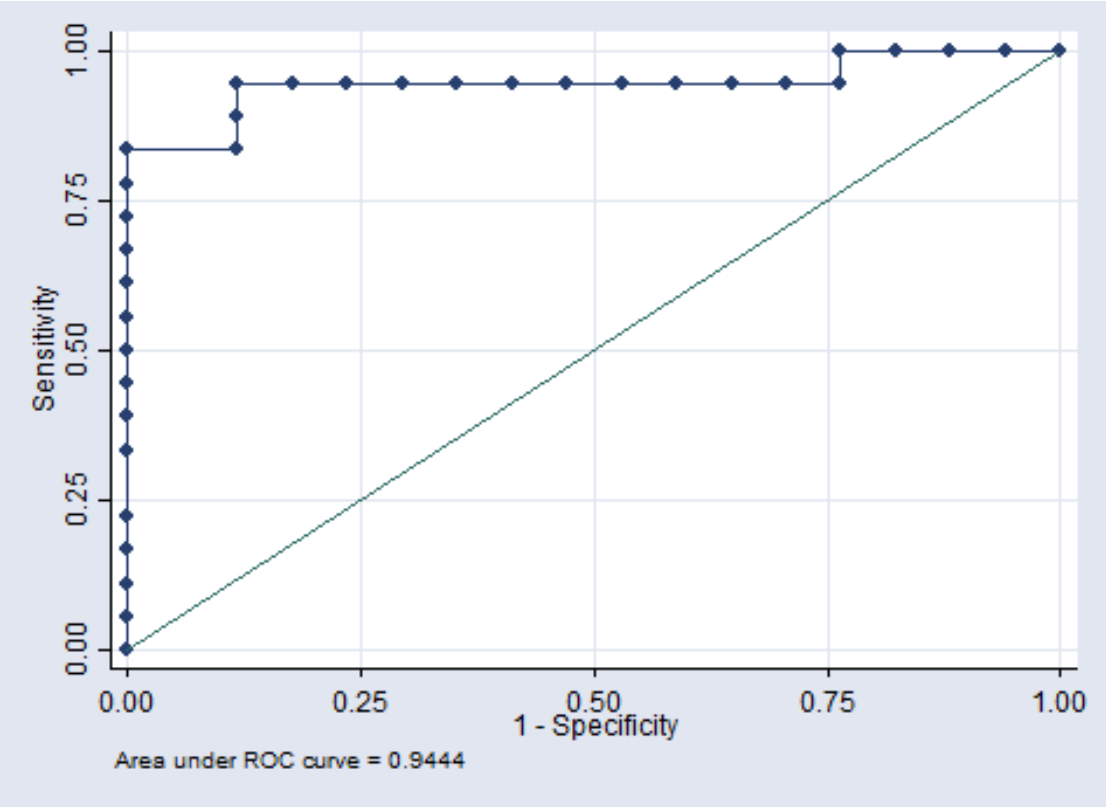


Table 30: Cut-off value for differentiating between O-HTN group and POAG Group using Superior Papillary area (VdSPA) Vascular Density measurements

VdSPA	O-HTN group Vs. POAG group (95% Confidence Interval) (n = 35)			
	AUC (SE)	CUT-OFF (%)	SENSITIVITY	SPECIFICITY
	0.9444 (0.0442)	> 65.07 %	100.00%	83.33 %

VdSPA – Superior Papillary area Vascular Density measurements
O-HTN – Ocular Hypertension, POAG – Primary Open Angle Glaucoma
AUC – Area under Curve, SE – Standard Error

Therefore a VdSPA Vascular Density measurement above 65.07 % suggests likely to be O-HTN and below suggests likely to be POAG.

ROC Curve 10: ROC Curve of Inferior Papillary area (VdIPA) Vascular Density measurements (O-HTN Group Vs. POAG Group)

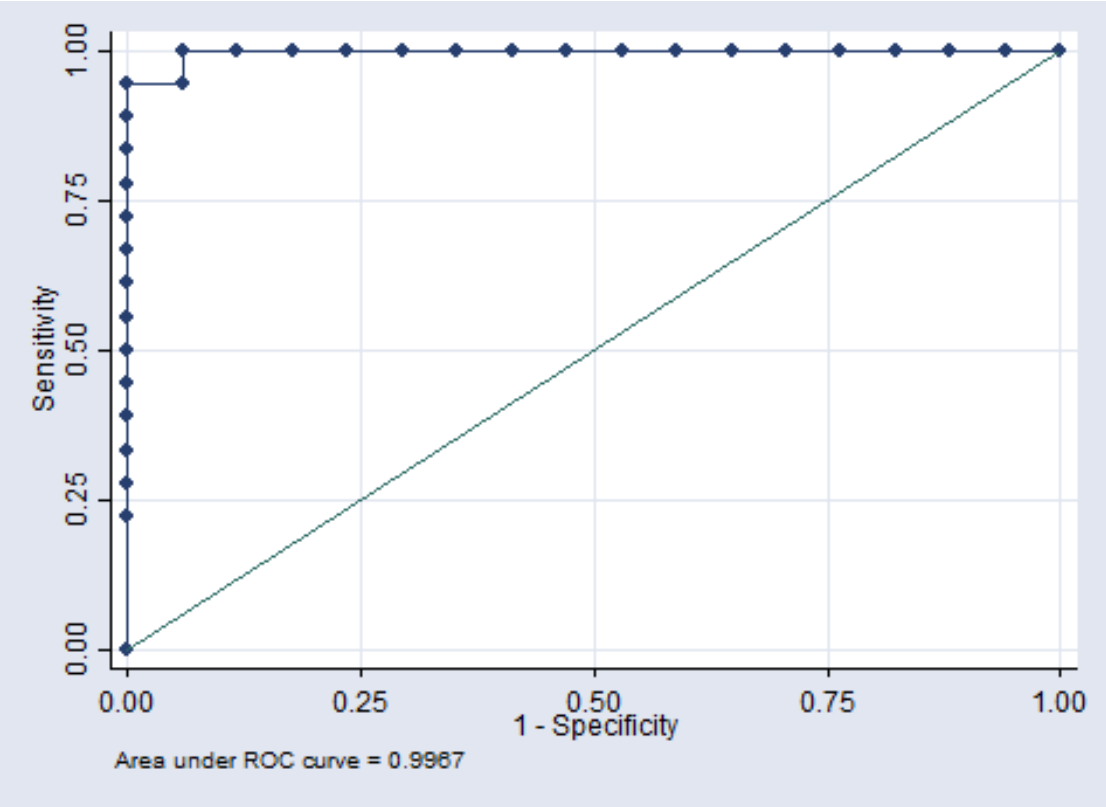


Table 31: Cut-off value for differentiating between O-HTN group and POAG Group using Inferior Papillary area (VdIPA) Vascular Density measurements

VdIPA	O-HTN group Vs. POAG group (95% Confidence Interval) (n = 35)			
	AUC (SE)	CUT-OFF (%)	SENSITIVITY	SPECIFICITY
	0.9967 (0.0046)	> 62.16 %	100.00%	94.44 %

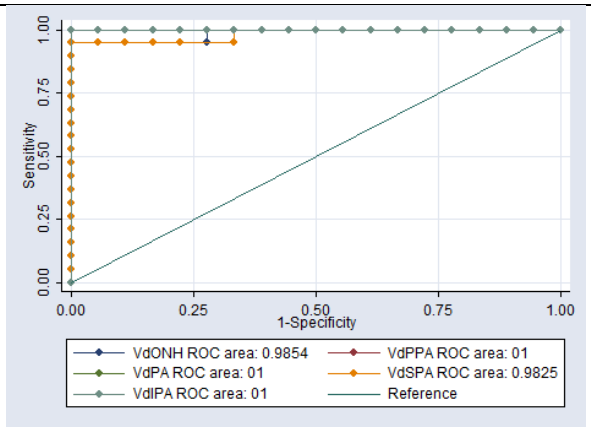
VdIPA – Inferior Papillary area Vascular Density measurements
O-HTN – Ocular Hypertension
POAG – Primary Open Angle Glaucoma
AUC – Area under Curve
SE – Standard Error

Therefore a VdIPA Vascular Density measurement above 62.16 % suggests likely to be O-HTN and below suggests likely to be POAG.

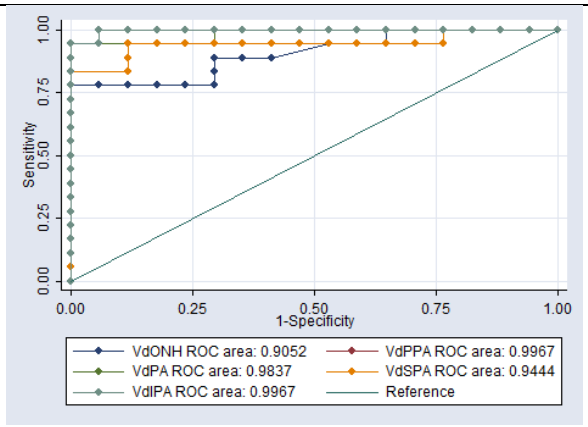
Table 32: Composite table showing Pairwise comparisons of Cut-off values of Vascular density measurements, to distinguish O-HTN from Normals and POAG Group

Area Of Interest	O-HTN Vs. Normals > = Normals < = O-HTN		O-HTN Vs. POAG > = O-HTN < = POAG	
	CUT-OFF	AUC (SE)	CUT-OFF	AUC (SE)
VdONH	> 69.73%	0.9854 (0.0157)	> 62.65%	0.9052 (0.0514)
VdPPA	> 69.01%	1.000 (0.000)	> 64.86 %	0.9967 (0.0046)
VdPA	> 71.42%	1.000 (0.000)	> 63.07 %	0.9837 (0.0175)
VdSPA	> 70.03%	0.9825 (0.0185)	> 65.07 %	0.9444 (0.0442)
VdIPA	> 72.42%	1.0000 (0.0000)	> 62.16 %	0.9967 (0.0046)

ROC Curve 11 and 12: Composite ROC Curves of all areas of interest studied in comparison between O-HTN Vs. Normals (Right) and O-HTN Vs. POAG (Left)



O-HTN Vs Normals



O-HTN Vs POAG

Table 33: Comparative representation of distribution of Retinal Nerve Fiber Layer Thickness (RNFL Thickness) and Vascular Density in Overall Papillary, Superior and Inferior Papillary areas in each group.

Area Of Interest	Normals (n = 19)		O-HTN (n = 18)		POAG (n = 17)	
	Mean of RNFL Thickness (μm)	Mean Vessel Density (%Area)	Mean of RNFL Thickness (μm)	Mean of Vessel Density (%Area)	Mean of RNFL Thickness (μm)	Mean of Vessel Density (%Area)
Papillary Area (Mean RNFL Thickness)	109.95	74.01 %	100.00	66.47 %	80.27	59.25 %
Superior Papillary Area (Superior RNFL Thickness)	134.63	73.10 %	125.89	66.28 %	98.53	59.72 %
Inferior Papillary Area (Inferior RNFL Thickness)	145.00	75.09 %	131.22	66.14 %	89.00	57.73 %

This table shows that, in the corresponding area of interest, as the RNFL thickness decreases, there is also a decrease in the Vessel Density measurement.

The above data sets, comprising of 54 eyes of 54 patients, include patients with Diabetes and Systemic Hypertension. These systemic co-morbidities have been known to produce vascular changes in end organs. Hence, excluding the patients with diagnosed Diabetes, Hypertension or both, from the original data set, we tabulated a separate dataset and the two data sets were compared for any differences in the vessel densities (Table 34).

Out of 54 patients, 8 had diabetes only, 10 had systemic hypertension only, and 6 had both diabetes and systemic hypertension. Therefore, excluding all these patients from the overall dataset, the new dataset formed, has n = 30 patients.

The comparison between the two datasets did not show much difference in the vessel densities, in all the areas of interest.

Table 34: Comparison of the mean vascular densities between the old dataset (patients with DM and HTN), and the new dataset (No DM and HTN)

	Old Dataset (DM+, HTN+, DM & HTN+) (n = 54)	New dataset (DM-, HTN-, DM & HTN -) (n = 30)
Mean VdONH (± SD) (%Area)	65.60 % (± 6.56)	66.68 % (± 7.01)
Mean VdPPA (± SD) (%Area)	66.88 (± 6.47)	68.09 % (± 6.95)
Mean VdPA (± SD) (%Area)	66.85 (± 6.40)	68.23 % (± 6.59)
Mean VdSPA (± SD) (%Area)	66.61 (± 6.00)	67.49 % (± 6.47)
Mean VdIPA (± SD) (%Area)	66.64 (± 7.44)	68.09 % (± 7.65)

It is therefore likely that in our group of patients, diabetes and hypertension did not have a significant effect on the retinal vasculature and can be ignored as a potential confounding factor in analysis and conclusions.

DISCUSSION

Glaucoma is a major cause of blindness in India and worldwide. On the basis of available data, there are about 11.2 million people in India, aged 40 years and above, who are diagnosed cases of glaucoma. Primary open angle glaucoma has a prevalence of 6.48 million and the estimated number of primary angle closure glaucoma is 2.54 million. (68).

The burden on society, due to glaucoma as a disease, is monumental, and one is of the opinion that the current prevalence is a gross underestimation of the real picture. This is due to the lack of a reliable, easy to perform, non-invasive test to detect cases, before substantial ocular morbidity has already occurred. Newer strategies need to be evolved to increase the efficiency and effectiveness of risk and disease identification in these patients. The good thing about glaucoma is that, if the disease is identified early enough, and the pathological process halted, or even slowed down, the patient's sight can be saved to give him or her functional vision for the rest of their lives. Hence, the need for a reliable, non-invasive, investigative modality, which detects the disease early, cannot be overemphasized.

Optical coherence tomography is a new imaging modality, which has completely changed the way Ophthalmologists are approaching ocular disease. Previously, slit-lamps and bio-microscopy techniques empowered the ophthalmologist to directly visualize intraocular pathologies; examination of the

ocular fundus and the optic nerve head, with its size, shape, cupping, etc., was possible in a way, not seen in any other sub-specialty of medicine. But, Optical coherence tomography (OCT) imaging has taken this even further, and has made it possible for us to not only visualize all the above said structures, but also view deeper structures in cross-sections, like a histo-pathological section. The newer generation OCT machines use the swept source technology and produce clearer images with increased resolution and faster scanning speeds. OCT Angiography is a relatively newer technique that works using swept source technology, to generate volumetric angiography images, by detecting motion contrast. It can generate images delineating individual vascular plexus at different levels, providing information about the vascular perfusion at each layer of the retina.

According to the vascular theory of pathogenesis of glaucoma, a vascular dysregulation, leading to changes in the retinal microcirculation, is responsible for the derangement of perfusion to the optic nerve head and peri-papillary retina. (36-47). But, there is also the concept that retinal ganglion cell loss is the precursor to reduction in vessel caliber and density in the retinal microcirculation, because of the reduced metabolic demand leading to vasoconstriction. This is in agreement with the observation of retinal arterial narrowing in patients with non-glaucomatous optic atrophy (46, 49, 50, 62-64). Therefore, in the case of glaucoma, the golden question that begs to be asked is ‘Which came first; the chicken or the egg? The retinal ganglion cell loss or the

reduction in vessel density?'. In our quest for this answer, several studies have been conducted to analyze the retinal vascular bed, using various non-invasive and invasive techniques. The earlier studies tried using fluorescein angiography (FA) to study optic nerve head blood flow. (69, 70). But FA cannot be used on a regular basis to monitor patients for glaucoma because it is invasive and has its own side effects. Plus, there are also problems in accurate quantification of the deficit. Laser Doppler flowmetry and Laser speckle flowmetry are non-invasive techniques that have also been used to measure optic nerve head blood supply and they have demonstrated that there is significant reduction in the blood flow at the ONH in glaucomatous eyes (38, 47, 71).

Despite all the information available, we are yet to quantify the retinal micro vascular network density, by a technique which is non-invasive, accurate and easily reproducible. This is where OCT Angiography really shines through, by providing cross sectional images, with an accurate wire frame of the entire micro vascular network at each level.

The purpose of this study was to explore the use of OCT Angiography in Glaucoma, by using the TRITON swept source OCT in the Indian population. The use of OCT angiography in Glaucoma has not yet been fully evaluated and its use to study vessel density to diagnose glaucoma, and to differentiate it from that of glaucoma suspects has not been quantified. We conducted this study to

define parameters and cut-offs, to differentiate glaucoma cases from suspects and normal patients, in the Indian population.

In our study, we recruited patients under three arms, early primary open angle glaucoma (POAG) patients, ocular hypertensives and normal controls. We chose early POAG patients as we believe that ocular hypertensives may be part of a spectrum of disease, which ranges from normals at one end to early POAG, and beyond, at the other end.

There was no statistically significant difference in the sex or eye ratio between the three groups. But, even though there was no statistically significant difference in the age distribution among the participants ($p = 0.067$), we found that the patients belonging to the POAG group were in general, slightly older (Age ranging from 42 to 70 years). This is in agreement with several previous studies, which have found glaucoma to occur in a slightly older population (19, 72, 73).

As vascular perfusion to the optic nerve head depends on mean ocular perfusion pressure (MOPP), which is in turn a derivative of systemic blood pressure and intraocular pressure (74), we compared the MOPP of the patients between the three groups and we found that there was a statistically significant reduction in the MOPP from Normals to O-HTN group ($p = <0.01$) and POAG group. ($p = <0.01$). This is consistent with another study, which found a similar

trend in the MOPP between open angle glaucoma patients and normal controls. (75).

The Intraocular pressure (IOP) was measured at the time of evaluation of the patient and was compared between the three groups. In our sample groups, the difference between mean IOP in the O-HTN group and Normals was statistically significant ($p = <0.01$); and the difference between the mean IOP in the POAG group and Normals was also statistically significant ($p<0.01$). But the difference in mean IOP between the O-HTN group and POAG group was not significant statistically ($p=0.947$). One observation we found in our patients was that the O-HTN group had a slightly higher mean IOP than the POAG group. This is probably due to the fact that most of the patients recruited under the POAG group were already using Anti-glaucoma medications at the time of evaluation (94.12%) as compared to the O-HTN Group, which had fewer participants on IOP lowering medications at the time of examination (16.67%).

Vision assessment showed that patients of O-HTN and POAG have slightly worse visual acuity than the corresponding normals. The difference between mean BCVA in the O-HTN group and Normals was statistically significant ($p = <0.01$); and the difference between the mean BCVA in the POAG group and Normals was also statistically significant ($p = <0.01$). But the difference in mean BCVA between the O-HTN group and POAG group was not significant statistically ($p = 1.00$). This observation shows that, on close

evaluation, subtle changes in vision do exist, even in earlier stages of the disease. (Table 11)

On clinical evaluation of the optic nerve head, one striking feature that always gives us a clue to suspecting glaucoma is the cup to disc ratio (CDR). In our study, we found larger CDR in patients under the POAG group (Mean CDR 0.74), as compared to the normals (Mean CDR 0.35) and O-HTN group (Mean CDR 0.39). We found a statistically significant difference in the CDR between the Normals and POAG group ($p = <0.01$), and also between the O-HTN Group and POAG group ($p = <0.01$), but no statistically significant difference in the CDR between Normals and O-HTN Group. ($p = 0.754$). This is consistent with findings in another study where larger CDR's were associated with development of POAG and higher the CDR, more chance of the patient having POAG. (76).

The functional assessment of ganglion cell damage by visual field testing was done and machine calculated Global indices, i.e., the Mean Deviation and Pattern standard deviation were analyzed in each group. We found that there was a significant difference in the Visual Field Mean Deviation (MD) and Pattern Standard Deviation (PSD) between the Normals and POAG group ($p = <0.01$) and also a statistically significant difference between the O-HTN Group and POAG group ($p = <0.01$). But there was no statistically significant difference in the Visual Field Mean Deviation (MD) between Normals and O-

HTN Group. (p = 1.00). This is consistent with the fact that in the O-HTN group, the field changes have not yet started to manifest, which makes the indices comparable to that of normal patients, whereas the early POAG patients show significantly worse indices.

Next, we evaluated the optic nerve head and retinal nerve fiber layer (RNFL) thickness by using swept source optical coherence tomography (DRI-TRITON Plus). The DRI TRITON Plus is a multimodal imaging system. The same system can be used to capture fundus photos, with the area of interest set as the optic nerve head, for documentation and further follow up comparisons. It takes over 1,00,000 A scans/ second, which helps by producing clearer, crisper images of high resolution. This gave us information about the structural differences in the retinal nerve fiber thickness in the three groups. As the distribution of RNFL loss takes place in a segmental manner, we took into consideration the mean RNFL thickness as well as, subdividing the area as superior and inferior quadrants. We found that there was a significant difference in the Mean RNFL Thickness between the Normals and POAG group (p = <0.01) and also a significant difference between the O-HTN Group and POAG group (p = <0.01). In the Normals and O-HTN group, we found that the inferior RNFL thickness was greater than the superior quadrant, both being within the normal range for age of the patients, as also seen in another study done in the Indian population (77). Whereas, the reduction in the RNFL thickness seen in

the POAG group was consistent with RNFL loss following the ISNT rule, with inferior quadrant being more thinned than the superior quadrant.

One important finding in our study was that there was statistically significant difference in the Inferior RNFL Thickness between the Normals and O-HTN Group. ($p = 0.020$). From this, we postulate that, even though, in both, the Normals group and the O-HTN group, the Mean RNFL thickness is within the normal range for the population, there is still a significant reduction in the Inferior RNFL thickness in Ocular hypertensives, which may go un-noticed if the RNFL thickness data were to be assessed in isolation, without comparison. This has led us to believe that, in Ocular Hypertensives, even though the RNFL thickness is within normal range for the population (towards the lower end of normal), the thinning has already started, prior to detection.

Next, using the DRI-TRITON Plus, we captured OCT Angiography images of a 3 x 3 mm area, centered around the optic nerve head, and using custom grading software of the device, generated maps, to produce two-dimensional images by collapsing the micro vascular frameworks, of all the layers from the internal limiting membrane to the retinal pigment epithelium. This is one of the biggest advantages of OCT Angiography; to delineate the retinal micro vascular network at each and every level, in great detail. These images were edited and analyzed for each of the areas of interest (Optic nerve head, peri-papillary area, whole papillary area, superior quadrant and inferior

quadrant of the papillary area), to calculate the vessel density (in area percentage).

We compared the images and data from the three groups; normals, O-HTN, and early POAG group, to search for any significant differences, by performing paired analysis between the groups, for each of the specific areas of interest. Previously, various researchers have tried to analyze the Vessel densities in Normals Vs. POAG patients; Normals Vs. Glaucoma suspects Vs. POAG patients; and even divided the POAG patients into mild, moderate and severe groups. (57, 64, 65, 78 – 81). All these studies have used OCT angiography images of different area measurements, and either machine inbuilt analysis protocols or used external third party software applications, by different techniques, to analyze the images. Therefore, on review of these studies, we have found that absolute values of the vessel densities, when compared between the studies may vary depending on the technique used to analyze the OCT angiography vascular maps. But, one fact that was evident, is that there was a definite trend or pattern in the distribution of the vessel densities in the different populations, i.e., the vessel densities (Vd) were highest in the normals, and mildly reduced in the suspects (Ocular hypertensives) and were considerably reduced in the diseased (POAG) group.

In our study, firstly, we compared the vessel densities at the optic nerve head (VdONH) between the Normals, O-HTN group and POAG group;

measurements, in the descending order of percentage area of Vascular density, were, Normals > O-HTN > POAG Group (in that order) and the difference was statistically significant between all three groups. ($p<0.01$)

This was in agreement with other previous studies (57, 64, 65, 78 – 81). All the other areas of interest were also analyzed and there was a statistically significant difference in the vessel densities between the three groups, following the same trend. The normals had the highest densities, followed by the suspects (ocular hypertensives) and lastly the POAG patients, showing the least densities. This was also in agreement with the previous similar studies. (57, 64, 65, 78 – 81).

In a few studies, (57, 78), the machine itself comes with inbuilt image analysis protocols and software, which provides a vessel density measurement directly. This may be more accurate in measurements. In our study we were partly limited by the fact that the machine did not have software protocols to directly measure the vessel density, and the images had to be exported out of the machine and analyzed separately to deduce the vessel density. This manual method may give rise to few errors, but in order to overcome the same, we performed the measurements on the same site of interest, twice, separately and took the average of the two, before utilizing the data for analysis. This, we believe, may to some extent, minimize the errors involved.

In order to test the accuracy of each of the parameters to differentiate between normals, suspects (ocular hypertensives), and disease (POAG patients), we plotted the observations in each of the groups, for each area of interest, and by comparing the sensitivity and specificity at each point; we calculated a cut-off value for each of the parameters, by plotting Receiver Operating Characteristic (ROC) Curves. To differentiate O-HTN patients from normals, we found that the Peri-Papillary area (VdPPA), Papillary area (VdPA) and Inferior Papillary area (VdIPA) Vascular density measurements had the highest accuracy (AUC = 1.000), followed by Optic Nerve Head area (VdONH) (AUC = 0.9854) and Superior Papillary area (VdSPA) Vascular Density measurements (AUC = 0.9825). This is in agreement with the work done previously, by other researchers, who have found that, when the whole image or large area of the image is taken into account for measurement, as in the case of the papillary area being considered, there is a higher probability of including more of the vasculature and hence the differences are more apparent. (57)

Next, we compared the data in O-HTN group to early POAG group, and this also showed a similar trend. The Peri-Papillary area (VdPPA) (AUC = 0.9967), Inferior Papillary area (VdIPA) (AUC = 0.9967) and Papillary area (VdPA) (AUC = 0.9837) Vascular density measurements had the highest accuracy to differentiate between the two groups, and were found to be better than Superior Papillary area (VdSPA) (AUC = 0.9444) and Optic Nerve Head area (VdONH) (AUC = 0.9052) Vascular Density measurements.

Therefore, in our study, papillary and peri-papillary vessel density measurements have been found to have the highest accuracy in differentiating Normals, O-HTN patients and early POAG patients. Similar results have also been encountered in a few other studies (57, 64, 81) whereas the AUC values in some other studies for the same area of interest were slightly lower than our own values. (80). Few other studies have also shown that in addition to the papillary area, the superior papillary area vessel density also has a high accuracy to differentiate normals and O-HTN group. (65).

The reason for such a degree of variability in the results between the different studies may be the use of different machines to capture the images, the different protocols and image analysis techniques (machine in built or external third party). But finally, the majority of the studies done so far, including our own, concur that the papillary area vascular density and peri-papillary vessel density area measurements have the highest accuracy and diagnostic ability to classify a patient into normal, suspect (ocular hypertensive) or disease (POAG) group.

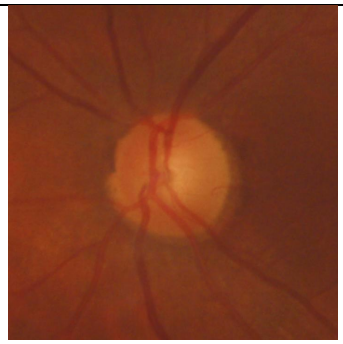
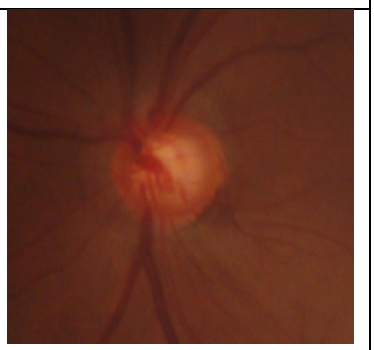
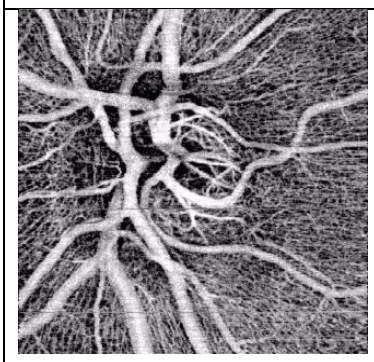
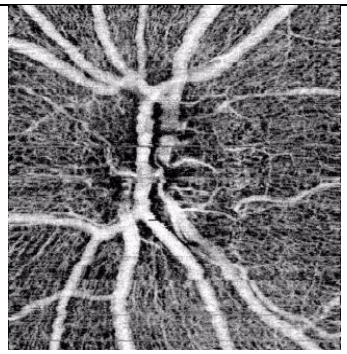
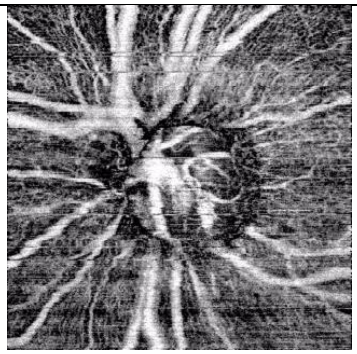
Our study population included patients who were known diabetics and hypertensives, diseases that are known to cause changes in the microvasculature throughout he body. Even though we have already excluded patients who have any form of retinopathy, we still wanted to assess whether our results would be

grossly different if we perform our analysis after excluding the diabetics and hypertensives. On doing so, and comparing our results from the previous data set (diabetics and hypertensives included) and the fresh data set (after excluding the diabetics and hypertensives), we found that there wasn't much difference between the two. Therefore, we concluded, it is likely that, in our group of patients, diabetes and hypertension did not have a significant effect on the retinal vasculature and could be ignored as a potential confounding factor in analysis and conclusions.

We also analyzed the correlation between the RNFL thickness and vessel density changes and we found that a lower RNFL Thickness was associated with a lower overall mean vessel density (papillary area vessel density). This was also correlating with the worsening of the global indices on automated perimetry, which was our yardstick in assessing functional deterioration.

Thus, at the end of our discussion, we come back to the question that set us out on this quest for truth; Which comes first, the RNFL thinning or the reduction in vascular density? In our study, in view of the analysis being cross-sectional by design, even through we were able to establish a significant link between RNFL loss and reduced vessel density, we are unable to establish a temporal cause-effect relationship of one to the other. This, though a limitation of our study, has given an idea about the prospects of future research.

In further studies, if one is able to follow up suspects, or even patients with risk factors for development of glaucoma, with serial vessel density measurements and RNFL thickness OCT scans or absolute retinal ganglion cell counts, and if this data is plotted against time, we may be able to establish a temporal relationship between the two. This may provide us with new information, which may improve our understanding of the disease and its pathogenesis and provide us with new treatment strategies, which will strengthen our armamentarium in this fight against the silent thief of sight that is glaucoma.

NORMAL	***OCULAR HYPERTENSION***	***EARLY PRIMARY OPEN ANGLE GLAUCOMA***
		
		

Colour Plate 22: Optic Disc photo and corresponding OCT-A image (Sample Image)

LIMITATIONS

- Cross-sectional study; therefore will not be able to assess for cause-effect relationship between vessel density and RNFL thinning.
- Vision was recorded in Snellen's format and had to be converted into LogMar for calculations.
- The patients in the Disease (POAG) group, even though statistically age matched, were slightly older than the patients in the normals group and O-HTN group
- Motion artifacts due to blinking or eye movement during image acquisition, caused a problem by producing poor quality images and the images had to be captured multiple times to get good quality images.

CONCLUSIONS

Using the DRI-TRITON Plus swept source optical coherence tomography machine, we can acquire high resolution OCT scans which provide information about, not only the retinal nerve fiber layer thickness, but also about the vessel density in the retinal microcirculation in all the layers of the retina. Our study shows that there is a significant relationship between the vessel density and the structural changes in the retina in glaucoma, in the form of RNFL thinning and functional changes in glaucoma, in the form of worsening Global indices on automated perimetry. We found that the Inferior RNFL thickness in the Ocular hypertension group, even though within normal limits, for age, was at the lower end of normal, and that there was a statistically significant difference between the normals and suspects (O-HTN group), which may be missed if only RNFL thickness is seen in isolation. We also found that papillary area and peri–papillary area vessel densities had the best diagnostic ability and accuracy to correctly differentiae the normals, suspects (O-HTN) and diseased (early POAG) groups, which were in agreement with other previous studies. Even though a significant relationship exists between RNFL loss and decrease in vessel density, further longitudinal studies are needed to establish a temporal cause-effect relationship between the two entities.

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ANNEXURE

1) PROFORMA

Study title: ANALYSIS OF RETINAL VASCULAR DENSITY USING OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY, TO DIFFERENTIATE HEALTHY, GLAUCOMA SUSPECT AND GLAUCOMATOUS EYES.

DATE: -

1. DEMOGRAPHICS

SERIAL NO: -

NAME HOSPITAL NO: -

AGE: -

SEX: - MALE / FEMALE

PHONE NO: -

ADDRESS: -

2.*CLINICAL EVALUATION - HISTORY*

OCULAR COMPLAINTS: -

PAST HISTORY (ANY OCULAR SURGERIES/ TREATMENT)

SYSTEMIC HISTORY

DM (YES / NO); If yes, duration

HTN (YES / NO); If yes, duration

IHD (YES / NO); If yes, duration

BRONCHIAL ASTHMA (YES / NO); If yes, duration

MEDICATION HISTORY (INCLUDING ANTI-GLAUCOMA MEDICATIONS)

ANTIGLAUCOMA MEDICATIONS:
Number of medications: -
Duration of use: -

3.*CLINICAL EVALUATION - EXAMINATION*

BLOOD PRESSURE (In millimeters of mercury): -

OCULAR PERFUSION PRESSURE (In millimetetrs of mercury): -

OCULAR EXAMINATION

OCULAR EXAMINATION	RIGHT EYE	LEFT EYE
VISION Unaided / Best Corrected Visual Acuity)	UNAIDED	UNAIDED
	BCVA	BCVA
ANTERIOR SEGMENT EXAMINATION		
	RIGHT EYE	LEFT EYE
IOP (In mm Hg)		
GONIOSCOPY (RP center grading)		

FUNDUS EXAMINATION	RIGHT EYE	LEFT EYE
DISC COLOUR SIZE SHAPE MARGINS		
VERTICAL DISC DIAMETER (in mm)		
CUP: DISC RATIO		
ARTERY: VEIN RATIO		
MACULA		
FOVEAL REFLEX		

4.INVESTATIGATIONS

I) CENTRAL CORNEAL THICKNESS (In micrometers)	RIGHT EYE	LEFT EYE

II) VISUAL FIELD TESTING BY HFA	RIGHT EYE	LEFT EYE
FIELD DEFECTS (IF ANY)		
MEAN DEVIATION (dB)		
PATTERN STANDARD DEVIATION (dB)		

III) OCT RNFL THICKNESS	RIGHT EYE	LEFT EYE
MEAN RNFL THICKNESS (in micrometres)		
SUPERIOR RNFL THICKNESS (in micrometres)		
INFERIOR RNFL THICKNESS (in micrometres)		

IV) OCT ANGIOGRAPHY VESSEL DENSITY (IN PERCENTAGE)	RIGHT EYE	LEFT EYE
OPTIC NERVE HEAD (%)		
PERIPAPILLARY AREA (%)		
PAPILLARY AREA (%)		
SUPERIOR PAPILLARY AREA (%)		
INFERIOR PAPILLARY AREA (%)		

2) PATIENT INFORMATION (English)

Study title: ANALYSIS OF RETINAL VASCULAR DENSITY USING OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY, TO DIFFERENTIATE HEALTHY, GLAUCOMA SUSPECT AND GLAUCOMATOUS EYES.

You are being invited to take part in this research study carried out in the Department of Ophthalmology, Schell Eye Hospital, Christian Medical College, Vellore. The information in this document is meant to help you decide whether or not to take part in this study.

Before you decide whether or not you wish to take part, you should read the information provided below carefully and, if you wish, discuss it with your relatives. Take time to ask questions – do not feel rushed or under pressure to make a quick decision.

You should clearly understand the risks and benefits of taking part in this study so that you can make a decision that is right for you. This process is known as 'Informed Consent'.

You do not have to take part in this study and a decision not to take part will not effect on your future medical care.

You can change your mind about taking part in the study any time you like. Even if the study has started, you can still opt out. You do not have to give us a reason. If you do opt out, it will not affect the quality of treatment you get in the future.

What is the purpose of the study?

Our study will assess the differences in microscopic circulation in the retina (the nerve of the eye), using a non-invasive investigative test, Optical coherence tomography angiography, between glaucoma suspects, and age matched normals (controls) and diagnosed early glaucoma patients. This angiography test is done with a machine, which takes pictures of the retina from outside (without any dye of injection being required to be given from outside). It is a painless and completely risk free test.

The volunteers with also be undergoing the routine, full eye examination and also the following additional tests, all of which are completely, non-invasive: -

- Central corneal thickness measurement

- Visual field testing with Automated visual field analyzer
- Retinal nerve fiber layer measurement, with Swept source OCT.

All these are routinely used tests in the evaluation of glaucoma.

Why have I been invited?

You have been chosen because you have fit one of the following criteria: -

- You are either a patient who has examination findings suspicious of glaucoma.
- Or, you are either a diagnosed patient of early glaucoma
- Or, you are chosen as a healthy volunteer, to be included in the control group.

What will happen if i take part?

If you take part in the study, you will be requested to provide the required clinical information and then undergo the routine eye examination and the required clinical investigations, which are non-invasive.

Expenses and payments?

There are no additional expenses or payments.

What are the possible benefits of taking part?

If you are a glaucoma suspect, then, the tests needed as part of evaluation, will be done free of cost, and if the results point towards glaucoma, then, we can plan for further management.

If you are already a diagnosed glaucoma patient, then, the clinical testing and investigations will be part of the regular follow up care. No additional investigations, other than those needed for routine follow up care, will be performed, and no extra cost will be levied on you. Additionally, by participating in this study, you will be helping future patients by helping to advance our understanding of the disease, which currently ails many others like yourself.

If you are a normal patient, recruited as a control, then you will be helping future patients, for whom newer treatment strategies may be developed as a result of better understanding of this disease.

What are the possible risks of taking part?

There are no risks involved in taking part in this study. All the examination procedures and investigations to be done are completely non-invasive and pain free.

Will my taking part be kept confidential?

All patient information is stored on password protected computer databases and in locked filing cabinets and will only be accessible to the research team.

What if there is a problem?

If you wish to complaint about any aspect of the way in which you have been approached or treated during the course of this study, you should contact the Principal investigator or you may contact Research Office, Carman Block, Bagayam, Vellore, 632002, email - research@cmcvellore.ac.in or researchothers@cmcvellore.ac.in, phone - 0416 2284294.

What will happen to any of my test results/samples I give?

The test results will be kept safe in the hospital's patient information databases, which are password protected and accessible to only the members of the research team, who are medical professionals.

How will the information I provide be used?

We plan to analyze the information collected and understand the disease condition, that is, glaucoma, in a better way. We will then publish the results in a health journal so others can read about it and learn from the results of the study, so that the new found information may be used to benefit others, the world over. The personal information collected will still remain strictly confidential, and only the interpretations of the data will be published.

Who has reviewed this study?

The Institutional Review Board (IRB) of the Christian Medical College, Vellore, has reviewed this study.

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical

history). By signing this document, you will be allowing the research team investigators, if required to access your medical information.

The results of clinical tests and therapy performed as part of this research may be included in your medical record. The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

Thank you for reading this.

If you agree to enter the study, please sign the attached consent form.

Contact Person (Principal Investigator)

Dr. Bharath Kumar. K

Department of Ophthalmology, Schell Campus,

Christian Medical College, Vellore.

Phone: 09600590205, email: bharathk1989two@gmail.com

3) INFORMED CONSENT FORM FOR SUBJECTS (English)

Study title: ANALYSIS OF RETINAL VASCULAR DENSITY USING OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY, TO DIFFERENTIATE HEALTHY, GLAUCOMA SUSPECT AND GLAUCOMATOUS EYES.

Study Number: _____

Subject's Name: _____

Date of Birth / Age: _____

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

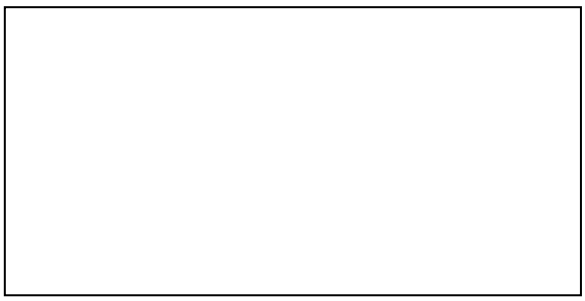
(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____ Signature:

Or



Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator &Name: _____

Date: _____/_____/_____

4) PATIENT INFORMATION (Tamil)

கிருஸ்துவ மருத்துவ கல்லூரி
வேலூர்.

நோயாளிக்கு ஆராய்ச்சி பற்றிய தகவல் தாள்

ஆராய்ச்சியின் பெயர் -

ANALYSIS OF RETINAL VASCULAR DENSITY USING OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY, TO DIFFERENTIATE HEALTHY, GLAUCOMA SUSPECT AND GLAUCOMATOUS EYES

இந்த ஆராய்ச்சியை பற்றிய முக்கியமான தகவல்களை தெரிந்துகொண்டு, இதில் பங்கேற்க உங்கள் சம்மதத்தை தெரிவிக்குமாறு நாங்கள் விடுத்த வேண்டுகோளை ஏற்றுக்கொண்டமைக்கு நன்றி. இந்த ஆராய்ச்சி சம்மந்தமான தகவல்கள், இதில் பங்கு பெறுவதினால் உங்களுக்கு ஏற்படக்கூடிய அசௌகரியங்கள், பாதிப்புகள் மற்றும் நன்மைகள் அனைத்தும் இப்படிவத்தில் கொடுக்கப்பட்டிருக்கின்றன. இதை நீங்களாகவே படித்து தெரிந்து கொள்ளலாம் அல்லது நீங்கள் விருப்பப்பட்டால், நாங்கள் இதை உங்களுக்கு படித்துக்காட்டி புரியும்படி சொல்வதற்கு தயாராக இருக்கிறோம். உங்களுக்கு ஏதேனும் புரியவில்லை என்றாலும் அல்லது கூடுதல் தகவல்கள் ஏதேனும் தேவை என்றாலும் நாங்கள் உங்களுக்கு உதவ தயாராக இருக்கிறோம்.

ஆராய்ச்சியில் பங்குபெற விரும்புபவர்களுக்கான தகவல்:

இந்த ஆராய்ச்சியின் நோக்கம் என்ன?

இந்த ஆராய்ச்சியின் நோக்கம் என்னவென்றால், கண்ணில் இருக்கும் விழித்திரை (Retina) எனப்படும் நரம்பின் நுண்ணிய இரத்த ஓட்டத்தை, ஆப்டிகல் கோஹெரன்ஸ் டோமோக்ராஃபி (OCT) என்ற கருவியை பயன்படுத்தி, கண் அழுத்த நோய் (Glaucoma) இருக்கலாம் என்ற சந்தேகத்திற்கு இடமானவர்கள், மற்றும், கண் அழுத்த நோய் முற்றிலும் இல்லாத ஆரோக்யமானவர்கள் மற்றும் ஆரம்ப கண் அழுத்த நோய் உறுதி செய்யப்பட்டுள்ளவர்கள் என்ற மூன்று பிரிவினருக்கும் அளக்கும் ஒரு சோதனை முயற்சி.

இந்த கருவியானது வெளியிலிருந்தே கண் விழித்திரை எனப்படும் ரெட்டினாவை எந்த சாயமோ, ஊசியோ இல்லாமல் புகைப்படங்கள் எடுக்கக்கூடியது.

இது ஒரு வலியில்லாத, ஊடுருவல் இல்லாத மற்றும் அபாயம் இல்லாத ஒரு சோதனை.

இந்த சோதனையில் பங்கேற்கும் தன்னார்வலர்களுக்கு வழக்கமான பரிசோதனைகள், முழு கண் பரிசோதனைகள் மற்றும் ஊடுருவல் இல்லாத கீழ்கண்ட சோதனைகளும் மேற்கொள்ளப்படும்:

- மத்திய கருவிழியின் (Cornea) தடிமனை அளவெடுத்தல்
- ஆடொமேடெட் விஷுவல் ஃபீல்ட் அனலைசர் மூலமாக காட்சி புலன் சோதனை
- ஆப்டிகல் கோஹெரன்ஸ் டோமோக்ராஃபி மூலமாக விழித்திரை நரம்பு நார் (Retinal Nerve Fiber) சோதனை.

இவை எல்லா சோதனைகளும் கண் அழுத்த நோய்க்கு வழக்கமாக மேற்கொள்ளப்படுபவை.

இந்த ஆராய்ச்சியில் பங்கு பெறுவதற்கு என்னை தேர்ந்தெடுக்க நீங்கள் விருப்பப்படுவதன் காரணமென்ன?

□ ஒன்று நீங்கள் கண் அழுத்த நோயாளியாக இருக்கலாம் என்ற சந்தேகத்திற்கு இடமானவர்கள் (Glaucoma Suspect)

□ இல்லையென்றால், நீங்கள் ஆரம்ப கண் அழுத்த நோய் உறுதி செய்யப்பட்டுள்ளவர்கள்

□ இல்லையென்றால், நீங்கள் கண் அழுத்த நோய் முற்றிலும் இல்லாத ஆரோக்யமான தன்னார்வலர்கள். நீங்கள் பாகுபாட்டுக்குழுவை சேர்ந்தவர்கள்.

இந்த ஆராய்ச்சியில் நான் கட்டாயம் பங்கு பெற வேண்டுமா?

இல்லை, இது உங்கள் விருப்பத்தை மட்டுமே பொறுத்தது. நீங்கள் விரும்பவில்லையெனில், உங்களை இந்த ஆராய்ச்சியில் ஈடுபடுத்தமாட்டார்கள். நீங்கள் இந்த ஆராய்ச்சியில் பங்கு பெறாவிட்டாலும், உங்களுக்கு கிடைக்கவேண்டிய மருத்துவ உதவி, எந்த பாரபட்சமும் இல்லாமல் தொடர்ந்து கிடைக்கும்.

இந்த ஆராய்ச்சியில் நான் பங்கேற்க வேண்டுமானால், நான் எடுத்துக் கொள்ள வேண்டிய பொறுப்புகள் என்ன?

சில எளிய பொறுப்புகளை எடுத்துக் கொள்ள வேண்டியிருக்கும்; அவையாவன:

- எங்களுக்குத் தேவையான மருத்துவ தகவல்களை தருதல்.
- வழக்கமான கண் பரிசோதனைக்கு உட்படுதல்
- கூடுதலாக ஊடுருவல் இல்லாத வேறு சில ஆய்வுகளுக்கு உட்படுதல்.

இந்த ஆராய்ச்சியில் பங்கு பெறுவதற்காக எனக்கு ஏதேனும் சன்மானம் வழங்கப்படுமா?

இல்லை, சன்மானம் ஏதும் வழங்கப்பட மாட்டாது.

இந்த ஆராய்ச்சியில் பங்கு பெறுவதினால் எனக்கோ, சமுதாயத்திற்கோ ஏதேனும் நன்மைகள் உண்டா?

அனேக நன்மைகள் உண்டு.

- தாங்கள் ஒரு கண் அழுத்த நோயாளியாக இருக்கலாம் என்ற சந்தேகத்திற்கு இடமானவர் என்றால், மேற்கண்ட சோதனைகள் இலவசமாக செய்யப்படும். அந்த பரிசோதனையின் முடிவுகள் மூலம் உங்களுக்கு கண் அழுத்த நோய் என்று உறுதி செய்யப்பட்டால், உங்களுடைய முந்தைய சிகிச்சையை வழி வகுப்போம்.
- தங்கள் ஏற்கனவே கண் அழுத்த நோயாளி என்று உறுதி செய்யப்பட்டிருந்தால், வழக்கமான பரிசோதனைகள் மேற்கொள்ளப்படும். வேறு எந்த கூடுதலான ஆய்வுகளும் மேற்கொள்ளப்படமட்டாது.கூடுதல் கட்டணமும் வசூலிக்கப்படாது. மேலாக, இந்த ஆராய்ச்சியில் பங்கேற்பதன் மூலம், எதிர் கால நோயாளிகளுக்கு, இந்த நோயால் ஏற்படப்போகும் விளைவுகளை முன்கூட்டியே தெரிந்து கொள்ள வழிவகுக்கும்.
- தாங்கள் பாகுபாட்டுக்குழுவை சேர்ந்த ஆரோக்யமானவரென்றால், இந்த ஆராய்ச்சியில் பங்கேற்பதன் மூலம், எதிர் கால நோயாளிகளுக்கு, புதுவகையான உத்திகளை கையாள்வது இந்த நோயால் ஏற்படப்போகும் விளைவுகளை முன்கூட்டியே தெரிந்து கொள்ள வழிவகுக்கும்.

இந்த ஆராய்ச்சியில் பங்கு பெறுவதினால் எனக்கு ஏதேனும் அசௌகரியங்கள், பாதிப்புகள் ஏற்படுமா?

பாதிப்புகளோ, அசௌகரியங்களோ ஏதும் ஏற்பட வாய்ப்பில்லை. ஏனென்றால் இங்கு மேற்கொள்ளப்படும் சோதனைகள் கொஞ்சம் கூட வலியில்லாத, ஊடுருவல் இல்லாத சோதனைகளாகும்.

இந்த ஆராய்ச்சியில் நான் பங்கு பெறுவதையும், என்னை குறித்த விவரங்களையும் வேறு யாருக்கும் தெரியாமல் இரகசியமாக வைக்கப்படுமா?

ஆம், இரகசியமாக வைக்கப்படும்.

நான் கொடுத்த தகவல்கள் எப்படி பயன்படுத்தப்படும்?

நாங்கள் ஆய்வு செய்து சேகரித்த தகவல்களை உபயோகித்து, கண் அழுத்த நோயின் நிலையை மேலும் சிறந்த முறையில் ஆய்வு மேற்கொள்ள திட்டமிட்டுள்ளோம். அதன் பின்பு, நாங்கள் சேகரித்த முடிவுகளை மருத்துவ பத்திரிக்கையில் வெளியிட்டு, மற்ற எல்லோரும் ஆராய்ச்சியின் முடிவுகளிலிருந்து பயனடைய வெண்டும் என்பதே குறிக்கோள். நோயாளியின் தனிப்பட்ட தகவல்கள் இரகசியமாக பாதுகாக்கப்படும்.

யார் இந்த ஆராய்ச்சியை மறு ஆய்வு செய்துள்ளனர்?

கிருஸ்துவ மருத்துவக் கல்லூரியின் நிறுவன மறு ஆய்வுக்குழு (IRB) இந்த ஆராய்ச்சியை மறு ஆய்வு செய்துள்ளது.

உங்களுக்கு உங்களுடைய தனிப்பட்ட தகவல்களின் பேரில் இரகசியத்தன்மைக்கு உரிமை உண்டு. இந்த ஆவணத்தில் கையொப்பமிடுவது மூலமாக, நீங்கள் எங்களுடைய ஆராய்ச்சிக்குழு ஆய்வாளர்களுக்கு உங்கள் மருத்துவ தகவல்களை அணுகுவதற்கு அனுமதி கொட்டுள்ளீர்.

எங்களுடைய மருத்துவ சோதனைகள் மற்றும் அளிக்கப்பட்ட சிகிச்சைகள் எல்லாமே உங்கள் மருத்துவ பதிவுகளில் சேர்க்கப்படலாம். இந்த ஆராய்ச்சியின் மூலம் கிடைக்கும் தகவல்கள் மருத்துவ பத்திரிக்கைகளில் பிரசுரிக்கப்பட்டால், தங்களின் பெயர் வெளியிடப்படாது.

இதை படித்ததற்கு மிக்க நன்றி.

உங்களுக்கு இந்த ஆராய்ச்சியில் கலந்து கொள்ள உடன்பாடெனில், இணைக்கப்பட்ட ஒப்புதல் பத்திரத்தில் கையொப்பமிடவும்.

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5) INFORMED CONSENT FORM FOR SUBJECTS (Tamil)

கிருஸ்துவ மருத்துவ கல்லூரி
வேலூர்.

ஆராய்ச்சியில் பங்குபெற ஒப்புதல் உறுதிமொழி அளிக்கும் படிவம்

ஆராய்ச்சியின் பெயர் -

ANALYSIS OF RETINAL VASCULAR DENSITY USING OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY, TO DIFFERENTIATE HEALTHY, GLAUCOMA SUSPECT AND GLAUCOMATOUS EYES

ஆராய்ச்சியின் எண்: _____

பங்கு பெரும் நபரின் பெயர்: _____-

பிரந்த தேதி/ வயது: _____

நான் இந்த ஆராய்ச்சியைப் பற்றிய முழுவிவரங்களையும் _____ தேதியிட்ட தாய் மொழியில் இருக்கும் ஆராய்ச்சி பற்றிய தகவல் தாளை படித்து முழுவதும் புரிந்து கொண்டேன். மற்றும் மேற்கண்ட ஆராய்ச்சியை பற்றி கேள்விகள் கேட்கின்ற வாய்ப்பும் எனக்கு அளிக்கப்பட்டது.

நடந்து கொண்டிருக்கும் ஆராய்ச்சி மற்றும் பின்னால் அதன் தொடர்பாக நடக்க போகும் ஆராய்ச்சி சம்பந்தப்பட்ட பதிவுகளை நான் ஆராய்ச்சியிலிருந்து விலகினாலும், நெரிமுறைகள் குழு மற்றும் ஒழுங்குமுறை அதிகாரிகள் பார்வையிட என்னுடைய அனுமதி தேவையில்லை.

என் சுய விருப்பத்துடனே நான் இந்த ஆராய்ச்சியில் பங்கு பெருகிறேன். இந்த ஆராய்ச்சியிலிருந்து என் சுய விருப்பப்படி, எந்த நேரமும் விலகிக் கொள்ள முடியும் என்றும், அதனால் இம்மருத்துவமனையில் எனக்கு கிடைக்கவேண்டிய மருத்துவ உதவிகள் அனைத்தும் எந்த பாரபட்சமும் இல்லாமல் தொடர்ந்து கிடைக்கும் என்றும் தெரிந்து கொண்டேன்.

இதில் பங்குபெற எனக்கு எந்தவித சன்மானமும் தரப்பட மாட்டாது என்றும் புரிந்துகொண்டேன்.

இந்த ஆராய்ச்சியின் முடிவுகள், என்னை பற்றிய தனிப்பட்ட தகவல் ஏதும் தராமல் இருந்தால், மருத்துவம் சார்ந்த பத்திரிக்கைகளில் பிரசுரமாவதற்கு எதிர்ப்பு தெரிவிக்கமாட்டேன்.

இந்த ஆராய்ச்சியில் பங்குபெற நான் என்ன செய்ய வேண்டும் என்று தெரிந்து கொண்டேன். அதன்படி ஆராய்ச்சியில் பங்கேற்று முழு ஒத்துழைப்பு கொடுக்க தயாராக உள்ளேன்.

பங்கு பெறுபவரின் கையொப்பம் _____ தேதி _____

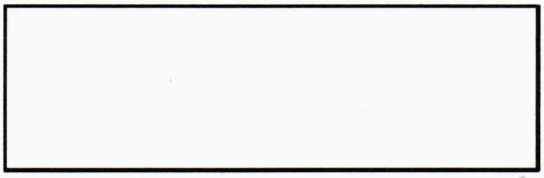
முகவரி : _____

_____

சாட்சியாளரின் கையொப்பம் _____ தேதி _____

முகவரி : _____

_____



ஆராய்ச்சியாளரின் கையொப்பம் _____ தேதி _____

6) *INSTITUTIONAL REVIEW BOARD APPROVAL*

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

May 14, 2018

Dr. Bharath Kumar. K,
PG Registrar,
Department of Ophthalmology,
Christian Medical College,
Vellore – 632 002.

Sub: **Fluid Research Grant NEW PROPOSAL:**
Analysis of retinal vascular density using optical coherence tomography angiography, to differentiate healthy, glaucoma suspect and glaucomatous eyes.
Dr. Bharath Kumar. K, Employment Number: 21342, P.G. Registrar, Ophthalmology, Dr. Andrew David Braganza, Employment Number: 14092, Professor, Dr. Lekha Mary Abraham, Employment Number: 20086, Professor, Dr. Arathi Simha, Employment number: 20217, Associate Professor, Department of Ophthalmology, Mr. John Michael, Employment Number: 52234, Optometrist., Dr B Antonisamy, Professor, Biostatistics.

Ref: IRB Min. No. 10892 [OBSERVE] dated 03.10.2017

Dear Dr. Bharath Kumar. K,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Andrew David Braganza, Dept. of Ophthalmology, CMC, Vellore

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

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INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

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Ref: IRB Min. No. 10892 [OBSERVE] dated 03.10.2017

Dear Dr. Bharath Kumar. K,

The Institutional Review Board **(Blue**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Analysis of retinal vascular density using optical coherence tomography angiography, to differentiate healthy, glaucoma suspect and glaucomatous eyes" on October 03rd 2017.

The Committee reviewed the following documents:

1. IRB application format
2. Information Sheet and Informed Consent Form (English, Tamil)
3. Cvs of Drs. Bharath Kumar. K, Andrew David Braganza, Lekha Mary Abraham, Arathi Simha, Mr. John Michael
4. No. of documents 1- 3

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on October 03rd 2017 in the C K Job Hall, Paul Brand Building, Christian Medical College, Vellore 632 004.

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

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Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Name	Qualification	Designation	Affiliation
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC, Vellore	Internal, Clinician
Dr. B. J. Prashantham	MA(Counseling Psychology), MA (Theology), Dr. Min (Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
Dr. Ratna Prabha	MBBS, MD (Pharma)	Associate Professor, Clinical Pharmacology, CMC, Vellore	Internal, Pharmacologist
Dr. Thomas V Paul	MBBS, MD, DNB, PhD	Professor, Endocrinology, CMC, Vellore	Internal, Clinician
Dr. Sowmya Sathyendra	MBBS, MD (Gen. Medicine)	Professor, Medicine III, CMC, Vellore	Internal, Clinician
Dr. Visalakshi. J	MPH, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Dr. Sathish Kumar	MBBS, MD, DCH	Professor, Child Health, CMC, Vellore	Internal, Clinician
Mrs. Emily Daniel	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Dr. Ajith Sivadasan	MD, DM	Professor, Neurological Sciences, CMC, Vellore	Internal, Clinician
Dr. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 00
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CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

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Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Dr. John Antony Jude Prakash	MBBS, MD	Professor, Clinical Microbiology, CMC, Vellore.	Internal, Clinician.

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of Withdrawals for the study entitled: "Analysis of retinal vascular density using optical coherence tomography angiography, to differentiate healthy, glaucoma suspect and glaucomatous eyes"on a monthly basis. Please send copies of this to the Research Office(research@cmcvellore.ac.in).

Fluid Grant Allocation:

A sum of 50,000/- INR (Rupees Fifty Thousand Only) will be granted for 6 Months.

Yours sincerely,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

CHRISTIAN MEDICAL COLLEGE VELLORE
Dr. BIJU GEORGE MBBS., MD., DM.
SECRETARY (ETHICS COMMITTEE)
Institutional Review Board
Christian Medical College, Vellore - 632 002.

IRB Min. No. 10892 [OBSERVE] dated 03.10.2017

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

7) DATA SHEET LEGEND

GROUP	1 – CONTROLS 2 – OCULAL HYPERTENSION 3 – PRIMARY OPEN ANGLE GLAUCOMA
EYE	1 – RIGHT 2 - LEFT
SEX	1 – MALE 2 - FEMALE
DM	1 – PRESENT 2 - ABSENT
HTN	1 – PRESENT 2 - ABSENT
IHD	1 – PRESENT 2 - ABSENT
BRONCHIAL ASTHMA	1 – PRESENT 2 - ABSENT
AGM(ANTI-GLAUCOMA MEDICATIONS)	1 – YES 2 - NO
CATARACT	1 – PRESENT 2 – ABSENT 3 - IOL
RAPD	1 – PRESENT 2 - ABSENT
GONIOSCOPY	0 – NO DIPPING 1 – DIPPING PRESENT

	2 – SCHWALBE'S LINE AND ANT 1/3rd OF TRAB MESHWORK SEEN 3 – MID 1/3RD OF TRAB MESHWORK 4 – POST 1/3RD OF TRAB MESHWORK 5 – SCLERAL SPUR 6 – CILIARY BODY BAND SEEN
DISC	1 – COLOUR, SIZE, SHAPE, MARGINS NORMAL 2 - COLOUR, SIZE, SHAPE, MARGINS ABNORMAL

MOPP	MEAN OCULAR PERFUSION PRESSURE (mm hg)
BCVA	BEST CORRECTED VISUAL ACUITY
RAPD	RELATIVE AFFERENT PUPILLARY DEFECT
IOP	INTRAOCULAR PRESSURE (mm hg)
VDD	VERTICAL DISC DIAMETER (millimeters)
CDR	CUP DISC RATIO
CCT	CENTRAL CORNEAL THICKNESS (micrometers)
MD	MEAN DEVIATION (decibels)
PSD	PATTERN STANDARD DEVIATION (decibels)
MRNFL	MEAN RETINAL NERVE FIBRE LAYER THICKNESS (micrometers)
SRNFL	SUPERIOR RETINAL NERVE FIBRE LAYER THICKNESS (micrometers)
IRNFL	INFERIOR RETINAL NERVE FIBRE LAYER THICKNESS (micrometers)
VdONH	VESSEL DENSITY – OPTIC NERVE HEAD (%)
VdPPA	VESSEL DENSITY – PERIPAPILLARY AREA (%)
VdPA	VESSEL DENSITY – PAPILLARY AREA (%)
VdSPA	VESSEL DENSITY – SUPERIOR PAPILLARY AREA (%)
VdIPA	VESSEL DENSITY – INFERIOR PAPILLARY AREA (%)

8) ***DATA SPREADSHEET***

SL.NO	GROUP	HOSPITAL NO	AGE	SEX	EYE	DM	DURATION(YRS)	HTN	DURATION(YRS)	IHD	DURATION(YRS)	BA	DURATION(YRS)
1	1	5648335	55	2	1	2		1	10	2		2	
2	1	6617075	33	2	2	2		2		2		2	
3	1	6622925	54	2	1	2		1	7	2		2	
4	1	6607915	51	2	1	2		2		2		2	
5	1	5548895	40	2	2	2		2		2		2	
6	1	6621555	37	2	1	2		2		2		2	
7	1	6607905	58	1	2	2		2		2		2	
8	1	3244315	68	2	1	1	8	1	8	2		2	
9	1	6622075	61	1	1	2		2		2		2	
10	1	6619015	35	2	1	2		2		2		2	
11	1	6623055	30	2	2	2		2		2		2	
12	1	2904785	64	1	2	1	10	2		2		2	
13	1	5016945	52	2	1	1	2	2		2		2	
14	1	6620905	52	1	1	2		2		2		2	
15	1	6626315	39	1	2	2		2		2		2	
16	1	3928435	66	2	2	2		2		2		2	
17	1	6621135	37	2	1	2		2		2		2	
18	1	2816775	56	1	1	2		2		2		2	
19	1	6620925	38	2	2	2		2		2		2	
20	2	2113805	52	2	2	1	1	2		2		2	
21	2	5668875	61	2	1	1	3	1	5	2		2	
22	2	5033615	30	2	2	2		2		2		2	
23	2	6358155	56	2	1	2		2		2		2	
24	2	966677E	70	2	2	1	1	2		2		2	
25	2	6265115	45	2	2	2		2		2		1	1
26	2	6376875	47	1	1	2		1	2	2		2	
27	2	6461025	38	1	1	2		2		2		2	
28	2	6461225	39	1	2	2		1	4	2		2	
29	2	6521475	57	1	1	2		2		2		2	
30	2	3799705	66	2	2	2		1	5	2		2	

SL NO	GROUP	HOSPITAL NO	AGE	SEX	EYE	DM	DURATION(YRS)	HTN	DURATION(YRS)	IHD	DURATION(YRS)	BA	DURATION(YRS)
31	2	1160265	61	1	2	2		1	1	2		2	
32	2	494528s	36	1	2	2		2		2		2	
33	2	548746s	30	2	2	2		2		2		2	
34	2	659665s	70	1	1	1	10	2		2		2	
35	2	649881s	59	1	2	1	5	2		2		2	
36	2	647762s	50	2	1	1	1	2		2		2	
37	2	478753s	68	2	2	1	4	1	4	2		2	
38	3	652077s	70	1	2	1	4	1	4	2		2	
39	3	152126s	52	1	2	2		2		2		2	
40	3	656176s	61	1	2	2		1	5	1	4	2	
41	3	654004s	70	1	1	2		2		2		2	
42	3	655258s	63	2	1	1	8	2		2		2	
43	3	6486315	67	2	1	2		2		2		2	
44	3	2808835	53	2	1	2		2		2		2	
45	3	6590035	56	1	2	2		2		2		2	
46	3	657125S	50	2	1	2		2		2		2	
47	3	643172S	45	1	2	2		1	2	2		2	
48	3	6581225	42	1	2	2		2		2		2	
49	3	647302s	50	1	1	2		2		2		2	
50	3	535749s	47	1	1	2		1	4	2		2	
51	3	561949s	67	1	2	2		2		2		2	
52	3	660882s	61	1	2	1	5	1	5	2		2	
53	3	565666s	70	2	2	1	6	1	6	1	3	2	
54	3	146899s	62	2	1	2		1	4	2		1	5

SL.NO	GROUP	HOSPITAL NO	AGM	NUMBER	MOPP	BVCA	CATARACT	RAPD	IOP	GONIO	DISC
1	1	564833S	2		50.66	0.00	1	2	14	5	1
2	1	661707S	2		51.11	0.00	1	2	10	5	1
3	1	662292S	2		54.22	0.00	2	2	12	5	1
4	1	660791S	2		57.77	0.00	2	2	10	5	1
5	1	554889S	2		54.22	0.00	2	2	12	5	1
6	1	662155S	2		52	0.00	2	2	12	5	1
7	1	660790S	2		53.77	0.00	1	2	16	5	1
8	1	324431s	2		57.33	0.00	1	2	14	5	1
9	1	662207s	2		52	0.00	3	2	12	5	1
10	1	661901S	2		44.88	0.00	2	2	16	5	1
11	1	662305S	2		55.11	0.00	2	2	14	5	1
12	1	290478S	2		60.44	0.00	1	2	16	5	1
13	1	501694S	2		50	0.00	2	2	15	5	1
14	1	662090S	2		57.33	0.00	2	2	14	5	1
15	1	662631S	2		55.11	0.00	2	2	14	5	1
16	1	392843S	2		63.55	0.00	1	2	8	5	1
17	1	662113S	2		52.88	0.00	2	2	14	5	1
18	1	281677S	2		58.66	0.00	2	2	12	5	1
19	1	662092S	2		51.55	0.00	2	2	16	5	1
20	2	211380S	1	2	53.11	0.20	1	2	29	5	1
21	2	566887S	2		56	0.20	2	2	26	5	1
22	2	503361S	2		50.66	0.00	3	2	24	5	1
23	2	635815S	2		48.44	0.20	3	2	24	5	1
24	2	966677E	1	1	44.44	0.00	1	2	30	5	1
25	2	626511S	2		41.33	0.20	1	2	28	5	1
26	2	637687S	2		40.44	0.20	1	2	26	5	1
27	2	646102S	2		42.66	0.00	2	2	26	5	1
28	2	646122S	2		53.77	0.00	2	2	26	6	1
29	2	652147S	2		33.77	0.00	2	2	36	5	1
30	2	379970S	1	2	44.44	0.20	2	2	30	5	1

SL.NO	GROUP	HOSPITAL NO	AGM	NUMBER	MOPP	BVCA	CATARACT	RAPD	IOP	GONIO	DISC
31	2	116026S	2		46.22	0.00	1	2	24	5	1
32	2	494528s	2		46.22	0.00	2	2	24	5	1
33	2	548746s	2		44	0.00	2	2	24	5	1
34	2	659665s	2		48	0.20	2	2	28	5	1
35	2	649881s	2		33.77	0.20	2	2	36	5	1
36	2	647762s	2		50.22	0.30	1	2	28	5	1
37	2	478753s	2		53.77	0.00	3	2	26	5	1
38	3	652077s	1	1	51.11	0.30	1	1	30	5	1
39	3	152126s	1	2	46.66	0.00	2	1	30	5	1
40	3	656176s	2		50.66	0.20	1	2	24	5	2
41	3	654004s	1	1	46.22	0.20	1	2	26	5	1
42	3	655258s	1	1	47.55	0.20	1	2	22	5	1
43	3	648631S	1	1	45.77	0.20	1	1	28	5	1
44	3	280883S	1	1	56.44	0.00	2	2	22	5	1
45	3	659003S	1	1	47.11	0.30	1	1	26	5	1
46	3	657125S	1	1	49.33	0.00	2	2	26	5	1
47	3	643172S	1	1	48.44	0.00	2	2	24	5	1
48	3	658122S	1	1	48.44	0.00	2	1	24	5	1
49	3	647302s	1	1	54.44	0.00	2	1	28	5	1
50	3	535749s	1	2	46.66	0.00	2	2	27	5	1
51	3	561949s	1	3	47.11	0.20	2	1	32	5	1
52	3	660882s	1	4	45.77	0.00	1	1	25	5	1
53	3	565666s	1	3	51.11	0.20	3	1	26	5	1
54	3	146899s	1	1	49.33	0.20	1	1	30	5	1

SL.NO	GROUP	HOSPITAL NO	VDD	CDR	CCT	MD	PSD	MRNFL	SRNFL	IRNFL	VdONH	VdPPA	VdPA	Vd5PA	VdIPA
1	1	5648335	2.09	0.4	508.00	-6.10	2.99	106.00	129.00	141.00	73.02	73.48	72.78	74.16	76.14
2	1	6617075	1.69	0.1	550.00	-4.68	1.46	115.00	159.00	130.00	72.64	75.19	75.18	77.41	72.42
3	1	6622925	1.95	0.3	529.00	-5.04	1.10	108.00	124.00	137.00	74.78	72.41	73.81	74.80	73.83
4	1	6607915	1.82	0.3	545.00	-4.31	2.27	107.00	127.00	135.00	71.91	78.48	76.87	78.11	76.88
5	1	5548895	1.87	0.5	491.00	-1.63	2.16	119.00	149.00	154.00	77.29	74.91	76.03	74.17	77.27
6	1	6621555	1.82	0.3	509.00	-4.56	1.93	100.00	109.00	141.00	73.80	74.74	74.80	71.97	77.65
7	1	6607905	1.82	0.4	501.00	-6.88	1.40	102.00	125.00	126.00	66.70	75.02	73.68	72.86	74.28
8	1	324431s	1.95	0.3	515.00	-3.19	2.66	104.00	127.00	146.00	74.72	72.90	73.37	70.57	76.04
9	1	662207s	1.65	0.3	538.00	-6.51	3.03	89.00	100.00	125.00	73.25	76.19	76.11	75.01	77.14
10	1	6619015	1.82	0.2	448.00	-5.63	1.27	104.00	122.00	135.00	70.95	72.26	71.75	68.29	74.64
11	1	6623055	1.95	0.3	485.00	-5.04	1.57	117.00	142.00	172.00	76.45	69.01	72.65	71.89	72.98
12	1	2904785	1.95	0.4	532.00	-6.04	1.37	112.00	148.00	147.00	69.73	72.15	71.42	70.03	72.59
13	1	5016945	1.95	0.4	492.00	-5.90	3.60	109.00	126.00	142.00	73.51	73.72	73.83	72.55	75.19
14	1	6620905	2.31	0.5	508.00	-5.04	1.10	105.00	123.00	137.00	74.53	75.71	73.73	74.56	75.10
15	1	6626315	2.08	0.5	491.00	-1.95	1.87	116.00	146.00	158.00	71.38	72.46	72.40	71.24	73.02
16	1	3928435	2.08	0.3	481.00	-6.04	1.37	112.00	144.00	147.00	71.36	75.61	74.22	75.02	74.71
17	1	6621135	2.21	0.4	510.00	-6.78	1.37	100.00	109.00	141.00	73.80	74.94	74.80	71.98	77.85
18	1	2816775	2.34	0.3	452.00	-0.26	1.81	142.00	195.00	182.00	74.53	73.43	74.32	71.37	73.50
19	1	6620925	1.98	0.4	471.00	-6.08	1.17	122.00	154.00	159.00	71.21	75.18	74.36	72.99	75.47
20	2	2113805	1.95	0.3	497.00	-4.46	4.13	96.00	129.00	132.00	60.35	65.80	63.07	62.49	61.67
21	2	5668875	1.95	0.5	508.00	-6.01	7.17	74.93	77.00	111.00	68.86	67.29	68.07	68.04	70.58
22	2	5033615	1.95	0.4	512.00	-3.07	1.86	109.00	150.00	127.00	68.84	67.20	69.72	66.20	67.46
23	2	6358155	1.95	0.5	513.00	-4.07	1.45	103.00	129.00	131.00	57.49	65.46	65.21	58.73	65.92
24	2	966677E	1.98	0.3	573.00	-4.19	2.67	94.00	112.00	129.00	66.26	67.49	67.95	68.31	65.42
25	2	6265115	2.21	0.7	503.00	-4.26	1.56	116.00	142.00	164.00	65.74	66.55	66.29	65.07	67.43
26	2	6376875	1.95	0.4	502.00	-2.12	1.87	75.00	107.00	110.00	64.91	66.22	66.62	65.26	67.22
27	2	6461025	1.82	0.2	502.00	-8.00	6.25	87.00	106.00	111.00	66.29	66.62	67.02	67.94	65.33
28	2	6461225	2.21	0.4	513.00	-6.01	1.31	122.00	149.00	146.00	64.04	68.90	66.14	65.17	67.56
29	2	6521475	1.82	0.2	544.00	-3.18	2.31	113.00	135.00	161.00	62.74	64.86	64.47	65.73	63.48
30	2	3799705	1.76	0.4	512.00	-6.55	1.93	104.00	134.00	127.00	66.88	68.24	68.96	68.31	66.88

SL.NO	GROUP	HOSPITAL NO	VDD	CDR	CCT	MD	PSD	MRNFL	SRNFL	IRNFL	VdONH	VdPPA	VdPA	VdSPA	VdIPA
31	2	1160265	1.95	0.5	582.00	-5.13	4.52	88.00	113.00	109.00	62.65	64.90	66.08	68.94	62.16
32	2	494528s	1.76	0.3	543.00	-4.13	1.20	109.00	132.00	143.00	68.94	66.66	67.67	66.70	67.44
33	2	548746s	1.76	0.3	499.00	-4.29	2.48	107.00	144.00	135.00	66.02	68.20	68.22	69.21	68.63
34	2	659665s	1.98	0.6	533.00	-0.77	2.36	92.00	111.00	121.00	66.88	65.24	67.65	66.30	65.88
35	2	649881s	1.69	0.2	628.00	-3.48	2.03	101.00	121.00	131.00	64.60	66.80	67.18	69.73	64.61
36	2	647762s	1.95	0.5	491.00	-4.45	1.39	102.00	134.00	129.00	59.21	68.29	66.14	68.69	66.00
37	2	478753s	1.82	0.3	533.00	-6.55	1.93	107.00	141.00	145.00	60.38	63.06	60.09	62.17	66.76
38	3	652077s	1.76	0.7	505.00	-9.86	5.06	65.00	57.00	89.00	56.17	63.32	62.55	62.53	61.98
39	3	152126s	2.2	0.8	499.00	-10.47	4.89	57.00	58.00	72.00	60.54	62.30	63.02	62.11	61.52
40	3	656176s	1.82	0.7	499.00	-11.13	10.25	83.00	101.00	97.00	60.92	61.43	62.74	61.10	59.23
41	3	654004s	2.21	0.8	532.00	-6.53	2.33	70.35	70.00	98.00	61.90	60.93	61.20	62.53	59.79
42	3	655258s	1.95	0.7	482.00	-7.83	1.98	94.00	123.00	83.00	61.95	60.47	59.92	60.67	58.50
43	3	6486315	2.09	0.8	461.00	-7.33	2.54	97.00	134.00	92.00	60.17	55.68	57.74	59.41	54.53
44	3	2808835	1.95	0.6	498.00	-6.60	3.48	88.00	118.00	104.00	54.08	60.36	59.74	59.13	58.79
45	3	6590035	1.65	0.8	394.00	-11.22	11.41	79.20	113.00	82.00	55.77	61.73	59.70	59.21	57.68
46	3	6571255	2.47	0.8	572.00	-8.36	6.38	94.00	135.00	80.00	59.21	56.54	57.12	59.75	57.06
47	3	6431725	1.65	0.7	532.00	-6.99	4.86	96.00	126.00	111.00	56.96	58.95	56.22	58.83	56.10
48	3	6581225	1.95	0.8	565.00	-6.36	3.75	62.00	82.00	72.00	58.50	59.41	59.63	60.35	57.91
49	3	647302s	1.82	0.7	507.00	-7.70	4.07	88.00	108.00	98.00	55.08	60.76	60.74	59.53	58.03
50	3	535749s	1.65	0.6	491.00	-8.73	5.21	90.00	98.00	91.00	59.17	54.68	56.74	58.41	53.53
51	3	561949s	1.98	0.7	538.00	-7.87	2.31	76.00	74.00	113.00	59.21	56.43	58.63	56.31	58.69
52	3	660882s	1.82	0.8	473.00	-9.88	5.90	67.00	83.00	80.00	59.28	56.67	57.42	59.79	57.36
53	3	565666s	2.2	0.7	522.00	-7.97	3.80	65.00	74.00	69.00	55.96	56.95	55.22	56.83	54.13
54	3	146899s	1.95	0.8	457.00	-7.79	4.25	93.00	121.00	82.00	60.95	59.47	58.92	58.67	56.50

9) SNELLEN VISUAL ACUITY TO LOGMAR VISUAL ACUITY CONVERSION TABLE

Snellen	LogMAR
6/60	1
6/48	0.9
6/38	0.8
6/30	0.7
6/24	0.6
6/19	0.5
6/15	0.4
6/12	0.3
6/9.5	0.2
6/7.5	0.1
6/6	0.0
6/4.8	-0.1
6/3.8	-0.2
6/3	-0.3